OBLON
SPIVAK
McCLELLAND
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&
NEUSTADT
P.C.
ATTORNEYS AT LAW

Docket No.: 217543US0CONT

COMMISSIONER FOR PATENTS
ALEXANDRIA, VIRGINIA 22313

RE: Application Serial No.: 10/029,871
Applicants: Yukio IINO, et al.
Filing Date: December 31, 2001
For: HETEROCYCLIC COMPOUNDS AND MEDICAL USE THEREOF
Group Art Unit: 1624
Examiner: PATEL, S.B.

SIR:

Attached hereto for filing are the following papers:

Certificate of Translation (Atsushi HAKODA), Certified English translation of International Application No. PCT/JP00/04298 filed June 29, 2000

Our check in the amount of **-0-** is attached covering any required fees. In the event any variance exists between the amount enclosed and the Patent Office charges for filing the above-noted documents, including any fees required under 37 C.F.R 1.136 for any necessary Extension of Time to make the filing of the attached documents timely, please charge or credit the difference to our Deposit Account No. 15-0030. Further, if these papers are not considered timely filed, then a petition is hereby made under 37 C.F.R. 1.136 for the necessary extension of time. A duplicate copy of this sheet is enclosed.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.

Stephen G. Baxter, Ph.D.
Registration No. 32,884

Vincent K. Shier, Ph.D.
Registration No. 50,552

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DOCKET NO.: 217543US0CONT

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

IN RE APPLICATION OF:	:
Yukio IINO, ET AL	: EXAMINER: PATEL, S.B.
SERIAL NO. : 10/029,871	:
FILED: DECEMBER 31, 2001	: GROUP ART UNIT: 1624

FOR: HETEROCYCLIC COMPOUNDS AND MEDICAL USE THEREOF

LETTER TO PTO

COMMISSIONER FOR PATENTS
ALEXANDRIA, VA 22313-1450

SIR:

Further to the Amendment and Request for Reconsideration filed on November 21, 2003 and in response to the Official Action dated May 21, 2003, Applicants respectfully submit herewith a certified English translation of International Application No. PCT/JP00/04298, filed on June 29, 2000.

Applicants note that Luzzio et al, used as the basis for an anticipation rejection in the Office Action dated May 21, 2003, published on December 13, 2001. In contrast, the present application was filed as International Application No. PCT/JP00/04298 on June 29, 2000, which is nearly 18 months prior to the publication of Luzzio et al.

In view of the submission of the certified English translation of International Application No. PCT/JP00/04298, filed on June 29, 2000, Applicants request that the Office acknowledge their claim to priority under 35 U.S.C. §120. In view of this acknowledgement, Applicants submit that Luzzio et al should not be available as a reference and the rejection over this reference should be withdrawn.

Applicants request acknowledgement that the rejection of Claims 1, 2, and 18-20 under 35 U.S.C. §102(a) over Luzzio et al has been withdrawn.

Applicants submit that the present application is now in condition for allowance. Early notification of such action is earnestly solicited.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.

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CERTIFICATE OF TRANSLATION

I, Atsushi HAKODA, Patent Attorney of NAKAMURA & PARTNERS, 3-1, Marunouchi 3-Chome, Chiyoda-Ku, Tokyo, Japan, hereby certify that to the best of my knowledge and belief the attached English translation is a true translation, made by me and for which I accept responsibility, of the PCT application number PCT/JP00/04298, filed in Japan on June 29, 2000, in the name of AJINOMOTO CO., INC..

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Atsushi Hakoda

Atsushi HAKODA
Patent Attorney

Dated: November 25, 2003

特許協力条約に基づく国際出願願書　　YIH0653

原本（出願用）－印刷日時 2000年06月29日（29.06.2000）木曜日 10時08分25秒

0	受理官庁記入欄	
0-1	国際出願番号.	
0-2	国際出願日	
0-3	(受付印)	

0-4	様式-PCT/RO/101 この特許協力条約に基づく国際出願願書は、	
0-4-1	右記によって作成された。	PCT-EASY Version 2.90 (updated 10.05.2000)
0-5	申立て 出願人は、この国際出願が特許協力条約に従って処理されることを請求する。	
0-6	出願人によって指定された受理官庁	日本国特許庁（RO/JP）
0-7	出願人又は代理人の書類記号	Y1H0653
I	発明の名称	~~複素環化合物及びその医薬用途~~ Heterocyclic Compounds and Medical Use thereof
II	出願人	
II-1	この欄に記載した者は	出願人である（applicant only）
II-2	右の指定国についての出願人である。	米国を除くすべての指定国（all designated States except US）
II-4ja	名称	味の素株式会社
II-4en	Name	AJINOMOTO CO.,INC.
II-5ja	あて名:	104-0031 日本国 東京都 中央区 京橋１丁目１５番１号
II-5en	Address:	15-1,Kyobashi 1-Chome, Chuo-Ku, Tokyo 104-0031 Japan
II-6	国籍（国名）	日本国 JP
II-7	住所（国名）	日本国 JP

特許協力条約に基づく国際出願願書

YIH0653

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II-6	国籍（国名）	日本国 JP
II-7	住所（国名）	日本国 JP

特許協力条約に基づく国際出願願書 Y1H0653

原本（出願用）- 印刷日時 2000年06月29日 (29.06.2000) 木曜日 10時08分25秒

III-1	その他の出願人又は発明者	
III-1-1	この欄に記載した者は	出願人及び発明者である (applicant and inventor)
III-1-2	右の指定国についての出願人である。	米国のみ (US only)
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III-1-7	住所（国名）	日本国 JP
III-2	その他の出願人又は発明者	
III-2-1	この欄に記載した者は	出願人及び発明者である (applicant and inventor)
III-2-2	右の指定国についての出願人である。	米国のみ (US only)
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特許協力条約に基づく国際出願願書
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YIH0653

III-3	その他の出願人又は発明者	
III-3-1	この欄に記載した者は	出願人及び発明者である (applicant and inventor)
III-3-2	右の指定国についての出願人である。	米国のみ (US only)
III-3-4ja	氏名(姓名)	小平 有子
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III-3-7	住所（国名）	日本国 JP
III-4	その他の出願人又は発明者	
III-4-1	この欄に記載した者は	出願人及び発明者である (applicant and inventor)
III-4-2	右の指定国についての出願人である。	米国のみ (US only)
III-4-4ja	氏名(姓名)	畑中 敏宏
III-4-4en	Name (LAST, First)	HATANAKA, Toshihiro
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III-4-7	住所（国名）	日本国 JP

III-5	その他の出願人又は発明者	
III-5-1	この欄に記載した者は	出願人及び発明者である (applicant and inventor)
III-5-2	右の指定国についての出願人である。	米国のみ (US only)
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III-5-5ja	あて名:	210-0801 日本国 神奈川県 川崎市川崎区鈴木町 １－１ 味の素株式会社　医薬研究所内
III-5-5en	Address:	c/o Pharmaceutical Research Laboratories, AJINOMOTO CO., INC., 1-1, Suzuki-Cho, Kawasaki-Ku, Kawasaki-Shi, Kanagawa 210-0801 Japan
III-5-6	国籍（国名）	日本国 JP
III-5-7	住所（国名）	日本国 JP
III-6	その他の出願人又は発明者	
III-6-1	この欄に記載した者は	出願人及び発明者である (applicant and inventor)
III-6-2	右の指定国についての出願人である。	米国のみ (US only)
III-6-4ja	氏名(姓名)	小林 幹
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III-6-6	国籍（国名）	日本国 JP
III-6-7	住所（国名）	日本国 JP

III-7	その他の出願人又は発明者	
III-7-1	この欄に記載した者は	出願人及び発明者である (applicant and inventor)
III-7-2	右の指定国についての出願人である。	米国のみ (US only)
III-7-4ja	氏名(姓名)	小西 敦
III-7-4cn	Name (LAST, First)	KONISHI, Atsushi
III-7-5ja	あて名:	210-0801 日本国 神奈川県 川崎市川崎区鈴木町 １－１ 味の素株式会社　医薬研究所内
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III-7-6	国籍（国名）	日本国 JP
III-7-7	住所（国名）	日本国 JP
III-8	その他の出願人又は発明者	
III-8-1	この欄に記載した者は	出願人及び発明者である (applicant and inventor)
III-8-2	右の指定国についての出願人である。	米国のみ (US only)
III-8-4ja	氏名(姓名)	山本 崇
III-8-4cn	Name (LAST, First)	YAMAMOTO, Takashi
III-8-5ja	あて名:	210-0801 日本国 神奈川県 川崎市川崎区鈴木町 １－１ 味の素株式会社　医薬研究所内
III-8-5cn	Address:	c/o Pharmaceutical Research Laboratories, AJINOMOTO CO., INC., 1-1, Suzuki-Cho, Kawasaki-Ku, Kawasaki-Shi, Kanagawa 210-0801 Japan
III-8-6	国籍（国名）	日本国 JP
III-8-7	住所（国名）	日本国 JP
IV-1	代理人又は共通の代表者、通知のあて名 下記の者は国際機関において右記のごとく出願人のために行動する。	代理人 (agent)
IV-1-1ja	氏名(姓名)	中村 稔
IV-1-1cn	Name (LAST, First)	NAKAMURA, Minoru
IV-1-2ja	あて名:	100-8355 日本国 東京都 千代田区 丸の内３丁目３番１号 新東京ビル６４６号
IV-1-2cn	Address:	Room 646, Shin-Tokyo Bldg, 3-1, Marunouchi 3-Chome, Chiyoda-Ku, Tokyo 100-8355 Japan
IV-1-3	電話番号	03-3211-8741
IV-1-4	ファクシミリ番号	03-3214-6358

特許協力条約に基づく国際出願願書
原本（出願用）- 印刷日時 2000年06月29日 (29.06.2000) 木曜日 10時08分25秒

YIH0653

IV-2	その他の代理人	筆頭代理人と同じあて名を有する代理人 (additional agent(s) with same address as first named agent)
IV-2-1ja	氏名	大塚 文昭; 熊倉 禎男; 宍戸 嘉一; 竹内 英人; 今城 俊夫; 小川 信夫; 村社 厚夫; 西島 孝喜; 箱田 篤
IV-2-1en	Name(s)	OHTSUKA, Fumiaki; KUMAKURA, Yoshio; SHISHIDO, Kaichi; TAKEUCHI, Hideto; IMASHIRO, Toshio; OGAWA, Nobuo; MURAKOSO, Hiroo; NISHIJIMA, Takaki; HAKODA, Atsushi
V	国の指定	
V-1	広域特許 (他の種類の保護又は取扱いを求める場合には括弧内に記載する。)	AP: GH GM KE LS MW MZ SD SL SZ TZ UG ZW 及びハラレプロトコルと特許協力条約の締約国である他の国 EA: AM AZ BY KG KZ MD RU TJ TM 及びユーラシア特許条約と特許協力条約の締約国である他の国 EP: AT BE CH&LI CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE 及びヨーロッパ特許条約と特許協力条約の締約国である他の国 OA: BF BJ CF CG CI CM GA GN GW ML MR NE SN TD TG 及びアフリカ知的所有権機構と特許協力条約の締約国である他の国
V-2	国内特許 (他の種類の保護又は取扱いを求める場合には括弧内に記載する。)	AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH&LI CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
V-5	指定の確認の宣言 出願人は、上記の指定に加えて、規則4.9(b)の規定に基づき、特許協力条約のもとで認められる他の全ての国の指定を行う。ただし、V-6欄に示した国の指定を除く。出願人は、これらの追加される指定が確認を条件としていること、並びに優先日から15月が経過する前にその確認がなされない指定は、この期間の経過時に、出願人によって取り下げられたものとみなされることを宣言する。	
V-6	指定の確認から除かれる国	なし (NONE)
VI-1	先の国内出願に基づく優先権主張	
VI-1-1	先の出願日	1999年07月01日 (01.07.1999)
VI-1-2	先の出願番号	平成１１年特許願第１８７９５９
VI-1-3	国名	日本国 JP

特許協力条約に基づく国際出願願書

原本（出願用）－印刷日時 2000年06月29日 (29.06.2000) 木曜日 10時08分25秒

YIH0653

VI-2	先の国内出願に基づく優先権主張		
VI-2-1	先の出願日	2000年03月15日 (15.03.2000)	
VI-2-2	先の出願番号	特願２０００－７１７０６	
VI-2-3	国名	日本国 JP	
VII-1	特定された国際調査機関(ISA)	日本国特許庁 (ISA/JP)	
VIII	照合欄		
VIII-1	願書	用紙の枚数: 8	添付された電子データ: －
VIII-2	明細書	71	－
VIII-3	請求の範囲	10	－
VIII-4	要約	1	y1h0653.txt
VIII-5	図面	0	－
VIII-7	合計	90	
	添付書類	添付	添付された電子データ
VIII-8	手数料計算用紙	✓	－
VIII-9	別個の記名押印された委任状	✓	－
VIII-12	優先権証明書	優先権証明書 VI-1, VI-2	－
VIII-16	PCT-EASYディスク	－	フレキシブルディスク
VIII-17	その他	国際事務局の口座への振込を証明する書面	－
VIII-17	その他	納付する手数料に相当する特許印紙を貼付した書面	－
VIII-18	要約書とともに提示する図の番号		
VIII-19	国際出願の使用言語名:	日本語 (Japanese)	
IX-1	提出者の記名押印		
IX-1-1	氏名(姓名)	中村 稔	
IX-2	提出者の記名押印		
IX-2-1	氏名(姓名)	大塚 文昭	
IX-3	提出者の記名押印		
IX-3-1	氏名(姓名)	熊倉 禎男	
IX-4	提出者の記名押印		
IX-4-1	氏名(姓名)	宍戸 嘉一	
IX-5	提出者の記名押印		
IX-5-1	氏名(姓名)	竹内 英人	
IX-6	提出者の記名押印		
IX-6-1	氏名(姓名)	今城 俊夫	
IX-7	提出者の記名押印		
IX-7-1	氏名(姓名)	小川 信夫	

IX-8	提出者の記名押印	
IX-8-1	氏名(姓名)	村社 厚夫
IX-9	提出者の記名押印	
IX-9-1	氏名(姓名)	西島 孝喜
IX-10	提出者の記名押印	
IX-10-1	氏名(姓名)	箱田 篤

受理官庁記入欄

10-1	国際出願として提出された書類の実際の受理の日	
10-2 10-2-1 10-2-2	図面 : 受理された 不足図面がある	
10-3	国際出願として提出された書類を補完する書類又は図面であってその後期間内に提出されたものの実際の受理の日（訂正日）	
10-4	特許協力条約第11条(2)に基づく必要な補完の期間内の受理の日	
10-5	出願人により特定された国際調査機関	ISA/JP
10-6	調査手数料未払いにつき、国際調査機関に調査用写しを送付していない	

国際事務局記入欄

11-1	記録原本の受理の日	

Specification

Heterocyclic Compounds and Medical Use thereof

Background of the Invention

The present invention relates to a therapeutic agent for various kinds of inflammatory disease.

It is known that various inflammatory diseases, rheumatoid diseases, immunoreactive diseases, cancer metastasis and viral diseases are caused by the abnormal production of inflammatory cytokines and matrix metalloprotease and also by the increase in the expression of inflammatory cell adhesion molecules.

Although various medicines for these diseases were developed in the prior art, further development of a medicine having a stronger efficiency, higher safety and weaker side effects is demanded.

The pathophysiological states of various chronic inflammatory diseases are considered to be caused by the continuous production of inflammation mediators such as cytokines [particularly, inflammatory cytokines including IL-1, IL-2, IL-6, IL-8 and tumor necrosis factor (TNF)], adhesion molecules, tissue destroying enzymes (such as matrix metalloprotease), etc. by the continuous extracellular stimulation.

The inflammatory mediators are produced because the gene expression is activated by the extracellular stimulation. A substance having the most important role in this step is a transcription factor known as AP-1 or NF-kappa B. Namely, it is expected that when the activation of AP-1/NF-kappa B can be inhibited, the development of inflammation and the advance thereof into chronic stage can be prevented and that such a method will be a hopeful treatment of inflammatory diseases such as rheumatoid arthritis and various autoimmune

diseases.

Glucocorticoid hormone (GC) which strongly inhibits the activation of intracellular AP-1 and NF-kappa B has been used as a powerful anti-inflammatory agent and immunosuppressant. However, the use of GC as a medicine is limited because it has various side effects due to hormonic action thereof and it causes rebound phenomenon.

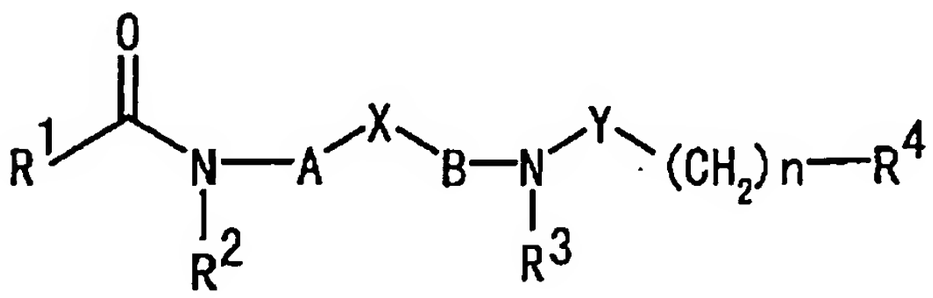
Disclosure of the Invention

An object of the present invention is to provide a new compound effective to cure chronic inflammatory disease with high activity and fewer side effects.

Another object of the present invention is to provide a pharmaceutical composition comprising corresponding new compound.

After intensive investigations made for the purpose of finding compounds having a strong activity of inhibiting the activation of AP-1 and NF-kappa B and useful as a strong remedy for chronic inflammatory diseases, the inventors have found that compounds of general formula (I) which will be described below have this effect. The present invention has been completed on the basis of this finding.

That is, the present invention provides a heterocyclic compound represented by the following general formula (I) or a pharmaceutically acceptable salt thereof.



(I)

wherein R^1 is a cycloalkyl group, a cycloalkyl group having a substituent(s), a

cycloalkenyl group or a cycloalkenyl group having a substituent(s); each R^2 and R^3 is a hydrogen atom or an alkyl group; R^4 is an alkyl group, an alkyl group having a substituent(s), an alkenyl group, an alkenyl group having a substituent(s), a cycloalkyl group, a cycloalkyl group having a substituent(s), a cycloalkenyl group, a cycloalkenyl group having a substituent(s), an aryl group, an aryl group having a substituent(s), an aromatic heterocyclic group having at least one hetero-atom within a ring or an aromatic heterocyclic group having a substituent(s) and at least one hetero-atom within a ring; A is a heterocyclic ring or a heterocyclic ring having a substituent(s); B is an aromatic ring, an aromatic ring having a substituent(s), a heterocyclic ring or a heterocyclic ring having a substituent(s); n is an integer selected from 0 to 6; -Y- is an interatomic bond, -CO-, -CO-O-, -CO-NR^5-, -CS-NR^6-, -SO-, -SO_2- wherein each R^5 and R^6 is a hydrogen atom or an alkyl group; and -X- is an interatomic bond, -O-, -O-CHR^7-, -CHR^8-O-, -O-CO-, -CO-O-, -O-CS-, -CS-O-, -S-, -SO-, -SO_2-, -S-CHR^9-, -CHR^{10}-S-, -S-CO-, -CO-S-, -S-CS-, -CS-S-, -SO_2-NR^{11}-, -NR^{12}-SO_2-, -NR^{13}-, -NR^{14}-CHR^{15}-, -CHR^{16}-NR^{17}-, -CO-, -C(=NOR^{18})-, -C(=CHR^{19})-,-CO-CHR^{20}-, -CHR^{21}-CO-, -CO-NR^{22}-, -NR^{23}-CO-, -$CR^{24}R^{25}$-, -CHR^{26}-CHR^{27}-, -CR^{28}=CR^{29}-, -O-CHR^{30}-CHR^{31}- wherein each R^7, R^8, R^9, R^{10}, R^{15}, R^{16}, R^{20}, R^{21}, R^{24}, R^{28}, R^{29}, R^{30} and R^{31} is either of a hydrogen atom or an alkyl group; each of R^{11}, R^{12}, R^{13}, R^{14}, R^{17}, R^{18}, R^{19}, R^{22} and R^{23} is either of a hydrogen atom, an alkyl group or an acyl group; each of R^{26} and R^{27} is either of a hydrogen atom, a hydroxy group or an alkyl group; and R^{25} is a hydrogen atom, a hydroxy group, an alkyl group, an alkyl group having a substituent(s), a mercapto group, an alkoxy group, an alkylthio group, an acyloxy group, an amino group, an alkylamino group, an amino group substituted with an amino protective group, a carboxyl group, an alkoxycarbonyl group, an aminocarbonyl group, or a cyano group.

Further, the present invention provides an AP-1 or NF-kappaB activation

production inhibitor and an inflammatory cell adhesion factor expression inhibitor, each of which comprises, as an active ingredient, the above-described heterocyclic compound or a pharmaceutically acceptable salt thereof, and these can be used as an anti-inflammatory agent, an anti-rheumatism agent, an immuno-suppressive agent, a cancer metastasis inhibitor, an antiviral agent or a curative agent for arterial sclerosis.

It is to be noted that a heterocyclic compound or a pharmaceutically acceptable salt thereof according to the present invention, in which R^1 is a cycloalkyl group having a substituent(s), may be more effective. Among these, compounds wherein R^1 is a cyclopropyl group having a substituent(s), more specifically either of a 2,2-dimethylcyclopropyl group or a 2,2-dichlorocyclopropyl group are of high activity. Among these, higher activity can be obtained by compounds wherein R^4 is 2,2-dimethylcyclopropyl group or 2,2-dichlorocyclopropyl group, -Y- is -CO- and n=0; or compounds wherein R^4 is an aryl group or an aryl group having a substituent(s), -Y- is -CO- and n=1; or compounds wherein R^4 is an aryl group or an aryl group having a substituent(s), -Y- is an interatomic bond and n is 1 or 2.

Best Mode for carrying out the Present Invention

Examples of the halogen atom in the present invention include a fluorine atom, a chlorine atom, a bromine atom and an iodine atom.

The alkyl group means a straight-chain or branched-chain alkyl group having 1 to 6 carbon atoms such as a methyl group, an ethyl group, a n-propyl group, an isopropyl group, a n-butyl group, an isobutyl group, a sec-butyl group, a tert-butyl group, a n-pentyl group, an isopentyl group, a tert-pentyl group, a neopentyl group, a 2-pentyl group, a 3-pentyl group, a n-hexyl group and a 2-hexyl

wherein the methyl group and the ethyl group are preferable.

The alkenyl group means a straight-chain or branched-chain alkenyl group having 1to 6 carbon atoms such as a 1-propenyl group, an allyl group, an isopropenyl group, a 1-butenyl group and a 2-butenyl group.

The cycloalkyl group means a cyclic alkyl group having 3 to 6 carbon atoms such as a cyclopropyl group, a cyclobutyl group, a cyclopentyl group and a cyclohexyl group, wherein the cyclopropyl group is a preferable cycloalkyl group.

The cycloalkenyl group means a cyclic alkenyl group having 3 to 6 carbon atoms such as a cyclopropenyl group, a cyclobutenyl group, a cyclopentenyl group and a cyclohexenyl group.

The hetero atom means specifically, for example, an oxygen atom, a sulfur atom and a nitrogen atom, wherein nitrogen atom is preferable.

The an aryl group means specifically, for example, a phenyl group, an indenyl group, a naphthyl group and a fluorenyl group, wherein phenyl group is preferable.

The aromatic heterocyclic group having at least one hetero atom means specifically, for example, a pyranyl group, a pyridyl group, a pyridazyl group, a pyrimidyl group, a pyrazyl group, a furyl group, a thienyl group, a pyrrolyl group, an oxazolyl group, an isoxazolyl group, a thiazolyl group, an isothiazolyl group, an imidazolyl group, a triazolyl group, a tertazolyl group, a pyrazolyl group, a furazanyl group, a thiadiazolyl group and a indolyl group, wherein pyridyl group, pyrimidyl group, imidazolyl group and triazolyl group are preferable, and among them pyridyl group is more preferable.

The acyl group means a formyl group, an acyl group having a straight-chain, a branched-chain or a cyclic alkyl group having 1 to 6 carbon atoms or an acyl group having a substituted or unsubstituted aryl group, and specifically, it includes, for example, a formyl group, an acetyl group, a propionyl group, a butyloyl group, an isobutyloyl group, a valeloyl group, an isovaleloyl group, a

pivaloyl group, a hexanoyl group, an acryloyl group, a metacryloyl group, a crotonoyl group, an isocrotonoyl group, a benzoyl group and a naphthoyl group.

The acyloxy group means a formyloxy group or an acyloxy group having a straight-chain, a branched chain or a cyclic alkyl group having 1 to 6 carbon atoms or an acyloxy group having an substituted or unsubstituted aryl group, and specifically, it includes, for example, a formyloxy group, an acetoxy group, a propionyloxy group, a butyloyloxy group, an isobutyloyloxy group, a valeloyloxy group, an isovaleloyloxy group, a pivaloyloxy group, a hexanoyloxy group, an acryloyloxy group, a metacryloyloxy group, a crotonoyloxy group, an isocrotonoyloxy group, a benzoyloxy group and a naphthoyloxy group.

The alkoxy group means an alkoxy group having a stragith chain, a branced chain or a ring alkyl group having 1 to 6 carbon atoms such as a methoxy group, an ethoxy group, a n-propoxy group, an isopropoxy group, a n-butoxy group, an isobutoxy group, a sec-butoxy group, a tert-butoxy group, a cyclopropyloxy group, a cyclobutoxy group, a cyclopentyloxy group and a cyclohexyloxy group, wherein methoxy group and ethoxy group are preferable.

The alkylthio group means an alkylthio group having a straight-chain, a branched-chain or a ring alkyl group having 1 to 6 carbon atoms such as a methylthio group, an ethylthio group, a n-propylthio group, an isopropylthio group, a n-butylthio group, a isobutylthio group, a sec-butylthio group, a tert-butylthio group, a cyclopropylthio group, a cyclobutylthio group, a cyclopentylthio group and a cyclobutylthio group.

The alkylamino group means an amino group mono-substituted or bi-substituted with alkyl group, the alkyl group including those having been specified in above description of the "alkyl group". Specifically, the alkylamino group includes, for example, an amino group, a methylamino group, an ethylamino group, a propylamino group, an isopropylamino group, a dimethylamino group, a

diethylamino group, a dipropylamino group, a diisopropylamino group and a methylethylamino group.

The amino protective group means a normally used protective group, including unlimitedly those substances that can protect the amino group against various reactions. Specifically, the amino protective group includes an acyl group such as a formyl group, an acetyl group and a pivaloyl group; and an alkoxycarbonyl group such as a methoxycarbonyl group, an ethoxycarbonyl group, a tert-butoxycarbonyl group and a (fluorene-9-yl) methoxycarbonyl group.

The alkoxycarbonyl group includes specifically, for example, methoxycarbonyl group, ethoxycarbonyl group, a propoxycarbonyl group, an isopropoxycarbonyl group, a n-butoxycarbonyl group, an isobutoxycarbonyl group, a sec-butoxycarbonyl group and a tert-butoxycarbonyl group.

In the description of R^1, the term "having a substituent(s)" in the expressions "a cycloalkyl group having a substituent(s)", "a cycloalkenyl group having a substituent(s)" and "a cyclopropyl group having a substituent(s)" means being substituted with at least one or more substituents, wherein the substituents may be the same or different and a position of the substituent(s) is not specifically limited but may be arbitrarily determined. Specifically, the term includes, for example, a halogen atom, an alkyl group, a substituted alkyl group, a carboxyl group, an alkoxycarbonyl group, a cyano group, an alkylamino group, and an amino group substituted with an amino protective group.

In the description of R^4, the term "having a substituent(s)" in the expression "an alkyl group having a substituent(s)" means being substituted with at least one or more substituents, wherein the substituents may be the same or different and a position of the substituent(s) is not specifically limited but may be arbitrarily determined. Specifically, the term includes, for example, a halogen atom, a hydroxy group, an alkoxy group, a carboxyl group, an alkoxycarbonyl group, a

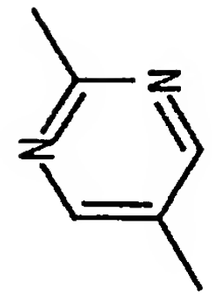
cyano group, an alkylamino group, and an amino group substituted with an amino protective group.

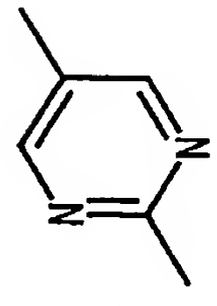
In the description of R^4, the term "having a substituent(s)" in the expressions "a cycloalkyl group having a substituent(s)" and "a cycloalkenyl group having a substituent(s)" means being substituted with at least one or more substituents, wherein the substituents may be the same or different and a position of the substituent(s) is not specifically limited but may be arbitrarily determined. Specifically, the term includes, for example, a halogen atom, a hydroxy group, an alkoxy group, a carboxyl group, an alkoxycarbonyl group, a cyano group, an alkylamino group, and an amino group substituted with an amino protective group.

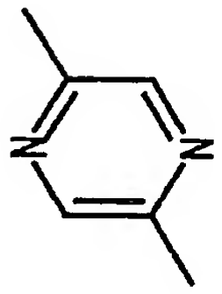
In the description of R^4, the term "having a substituent(s)" in the expressions "an aryl group having a substituent(s)" and "an aromatic heterocyclic group having one or more hetero atoms having a substituent(s)" means having one to three substituents on the ring, wherein the substituents may be the same or different and a position of the substituent(s) is not specifically limited but may be arbitrarily determined. Specifically, the term includes, for example, a halogen atom, an alkyl group, a substituted alkyl group, a hydroxy group, an alkoxy group, a carboxyl group, an alkoxycarbonyl group, a cyano group, an alkylamino group, and an amino group substituted with an amino protective group.

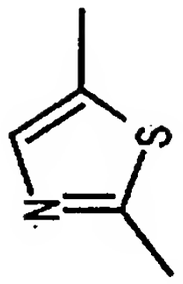
The term "heterocyclic ring" in the expression "a heterocyclic ring or a heterocyclic ring having a substituent(s)" in the description with reference to A and in "a heterocyclic ring or a heterocyclic ring having a substituent(s)" in the description with reference to B is used to mean a heterocyclic ring comprising a single ring or two rings with 5 to 7 members consisting of carbon and nitrogen, oxygen, sulfur and so on, and includes specifically, for example, pyridine, dihydropyran, pyridazine, pyrimidine, pyrazine, triazine, tetrazine, pyrrole, furan,

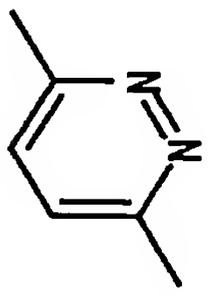
thiophene, oxazole, isoxazole, thiazole, isothiazole, imidazole, triazole, pyrazole, furazan, thiadiazole, pyrrolidine, piperidine, piperazine, indole, benzopyrazole, benzoxazole, benzothiazole, benzoimidazole, benzofuran, benzothiophene, pyrazolopyridine, quinoline, isoquinoline, naphthylidine and benzodiazepine. Preferably, the heterocyclic ring should be the one shown in the following diagram, and more preferably pyridine. It is to be noted that for those bonds in both sides with respect to A and B, i.e., the bonds of NR^2 and X with A and the bonds X and NR^3 with B, the bond positions of them are not limited but may be arbitrarily determined.

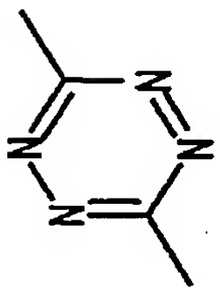


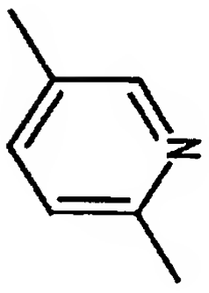


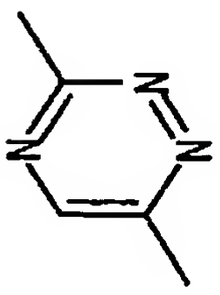


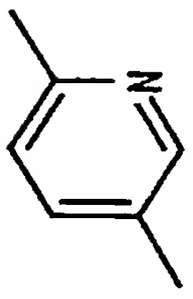


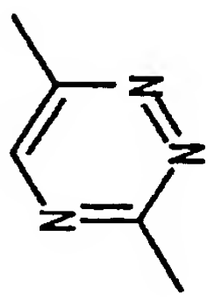












In the above formulas, the first two formulas are preferred.

The term "aromatic heterocyclic ring" in the expresion "an aromatic heterocyclic ring or an aromatic heterocyclic ring having a substituent(s)" in the description with reference to A and "an aromatic heterocyclic ring or an aromatic heterocyclic ring having a substituent(s)" in the description with reference to B

represents an unsaturated aromatic heterocyclic ring comprising a single ring or two rings with 5 to 7 members consisting of carbon and nitrogen, oxygen, sulfur and so on, and includes specifically, for example, pyridine, dihydropyran, pyridazine, pyrimidine, pyrazine, triazine, tetrazine, pyrrole, furan, thiophene, oxazole, isoxazole, thiazole, isothiazole, imidazole, triazole, pyrazole, furazan, thiadiazole, indole, benzopyrazole, benzoxazole, benzothiazole, benzoimidazole, benzofuran, benzothiophene, pyrazolopyridine, quinoline, isoquinoline, naphthylidyne and benzodiazepine.

The term "an aromatic ring" in the expression "an aromatic ring or an aromatic ring having a substituent(s)" in the description with reference to B represents an aromatic ring comprising a single ring or two rings consisting of carbon atoms, and includes specifically, for example, benzene, naphthalene, indene and naphthalene, wherein benzene is preferable. It is to be noted that the positions of the bonds at both sides with respect to B, i.e., the bonds with X and NR^3, are not specifically limited but may be arbitrary determined.

The term "having a substituent(s)" in the expression "a heterocyclic ring having a substituent(s)" in the description with reference to A and "an aromatic ring having a substituent(s)" in the description with reference to B means having one to three substituents on the ring, wherein the substituents may be the same or different and the position of the substituent(s) is not specifically limited but may be arbitrarily determined. Specifically, the term includes, for example, a halogen atom, an alkyl group, a substituted alkyl group, a hydroxy group, an alkoxy group, a carboxyl group, an alkoxycarbonyl group, a cyano group, an alkylamino group or an amino group substituted with an amino protective group.

As heterocyclic compounds represented by the general formula (I) in claim 1 and pharmaceutically acceptable salts thereof, the preferred are those wherein B is a phenylene group; R^1 is a cycloalkyl group having a substituent(s) or a

cycloalkenyl group having a substituent(s); R^2 is a hydrogen atom or an alkyl group; R^3 is a hydrogen atom or an alkyl group; R^4 is an alkyl group which may be substituted, a cycloalkyl group which may be substituted, a cycloalkenyl group which may be substituted, an aryl group which may be substituted or an aromatic heterocyclic ring group which may be substituted and also has one or more hetero atoms; -X- is -O-, -O-CHR^7-, -CHR^8-O-, -O-CO-, -CO-O-, -O-CS-, -CS-O-, -S-, -SO-, -SO_2-, -S-CHR^9-, -CHR^{10}-S-, -S-CO-, -CO-S-, -S-CS-, -CS-S-, -SO_2-NR^{11}-, -NR^{12}-SO_2-, -NR^{13}-, -NR^{14}-CHR^{15}-, -CHR^{16}-NR^{17}-, -CO-, -C(=NOR^{18})-, -C(=CHR^{19})-,-CO-CHR^{20}-, -CHR^{21}-CO-, -CO-NR^{22}-, -NR^{23}-CO-, -$CR^{24}R^{25}$-, -CHR^{26}-CHR^{27}- or -CR^{28}=CR^{29}- wherein R^7, R^8, R^9, R^{10}, R^{20}, R^{21}, R^{24}, R^{28} and R^{29} are either of a hydrogen atom or an alkyl group; R^{11}, R^{12}, R^{13}, R^{14}, R^{17}, R^{18}, R^{19}, R^{22} and R^{23} are either of a hydrogen atom, an alkyl group or an acyl group; R^{15} and R^{16} are a hydrogen atom or an alkyl group; R^{26} and R^{27} are either of a hydrogen atom, a hydroxy group or an alkyl group; R^{25} is a hydrogen atom, an hydroxy group, an alkyl group which may be substituted, a mercapto group, an alkoxy group, an alkylthio group, an acyloxy group, an amino group which may be substituted with an alkyl group or an amino protective group, a carboxyl group, an alkoxycarbonyl group, an aminocarbonyl group, or a cyano group); n is the integer selected from 0 to 6; Y is -C(O)-; and A is an aromatic heterocyclic ring including at least one or more nitrogen atom.

Further, as the heterocyclic compounds represented by the general formula (I) set out in claim 1 or pharmaceutically acceptable salt thereof, the following compounds are preferable.

Preferably, R^1 should be a cycloalkyl group having a substituent(s), more preferably a cyclopropyl group having a substituent(s), and most preferably either of a 2,2-dimethylcyclopropyl group, a 2,2-dichlorocyclopropyl group, a 2,2-difluorocyclopropyl group or a 2,2-dibromocyclopropyl group. Among them, 2,2-dimethylcyclopropyl group and 2,2-dichlorocyclopropyl group are especially

preferred.

In the case where R^1 is a 2,2-dimethylcyclopropyl group having a substituent(s), preferably an absolute configuration of the carbon atom on the cyclopropyl group adjacent to the carbonyl group should be S.

Preferably R^2 should be a hydrogen atom or a methyl group, and more preferably hydrogen atom.

Preferably R^3 should be a hydrogen atom or a methyl group, and more preferably hydrogen atom.

Preferably R^4 should be a cycloalkyl group having a substituent(s) or an aryl group having a substituent(s), more preferably cyclopropyl group having a substituent(s), and most preferably either of a 2,2-dimethylcyclopropyl group, a 2,2-dichlorocyclopropyl group, a 2,2-difluorocyclopropyl group or a 2,2-dibromocyclopropyl group. Further, among them, 2,2-dimethylcyclopropyl group and 2,2-dichlorocyclopropyl group are especially preferred.

In the case where R^4 is a 2,2-dimethylcyclopropyl group having a substituent(s), preferably the absolute configuration of the carbon atom on the cyclopropyl group adjacent to the carbonyl group should be S.

Further, in the case where each of R^1 and R^4 is a 2,2-dimethylcyclopropyl group having a substituent(s), preferably the absolute configuration of the carbon atoms on the cyclopropyl group of R^1 adjacent to the carbonyl group should be S for both.

Preferably, A should be either of an aromatic heterocyclic ring or an aromatic heterocyclic ring having a substituent(s), and more preferably either of a pyridine, a pyridazine, a pyrimidine, a pyridine having a substituent(s), a pyridazine having a substituent(s) or a pyrimidine having a substituent(s).

Preferably, B should be either of an aromatic ring, an aromatic ring having a substituent(s), an aromatic heterocyclic ring or an aromatic heterocyclic ring

having a substituent(s), and more preferably a benzene ring or a benzene ring having a substituent(s).

Preferably, X should be an interatomic bond, -O-, -O-CHR^{7}-, -CHR^{8}-O-, -S-, -NR^{13}-, -CR^{24}R^{25}- or -O-CHR^{30}-CHR^{31}- wherein R^{7}, R^{8}, R^{24}, R^{30} and R^{31} are either of a hydrogen atom or an alkyl group; R^{13} is either of a hydrogen atom, an alkyl group or an acyl group; and R^{25} is a hydrogen atom, a hydroxy group, an alkyl group, an alkyl group having a substituent(s), a mercapto group, an alkoxy group, an alkylthio group, an acyloxy group, an amino group, an alkylamino group, an amino group substituted with an amino protective group, a carboxyl group, an alkoxycarbonyl group, an aminocarbonyl group, or a cyano group); and more preferably -X- should be -O-, -O-CHR^{7}-, -CHR^{8}-O-, -S-, -NR^{13}- or -CR^{24}R^{25}- wherein R^{7}, R^{8}and R^{24} are either of a hydrogen atom or an alkyl group; R^{13} is either of a hydrogen atom, an alkyl group or an acyl group; and R^{25} is a hydrogen atom, a hydroxy group, an alkyl group which may be substituted, a mercapto group, an alkoxy group, an alkylthio group, an acyloxy group, an amino group which may be substituted with an alkyl group or an amino protective group, a carboxyl group, an alkoxycarbonyl group, an aminocarbonyl group, or a cyano group.

Preferably, Y should be an interatomic bond, -CO-, -CONR^{5}-, -CSNR^{6}- or -SO_2- wherein R^{5} and R^{6} are a hydrogen atom or an alkyl group, and more preferably Y should be -CO-.

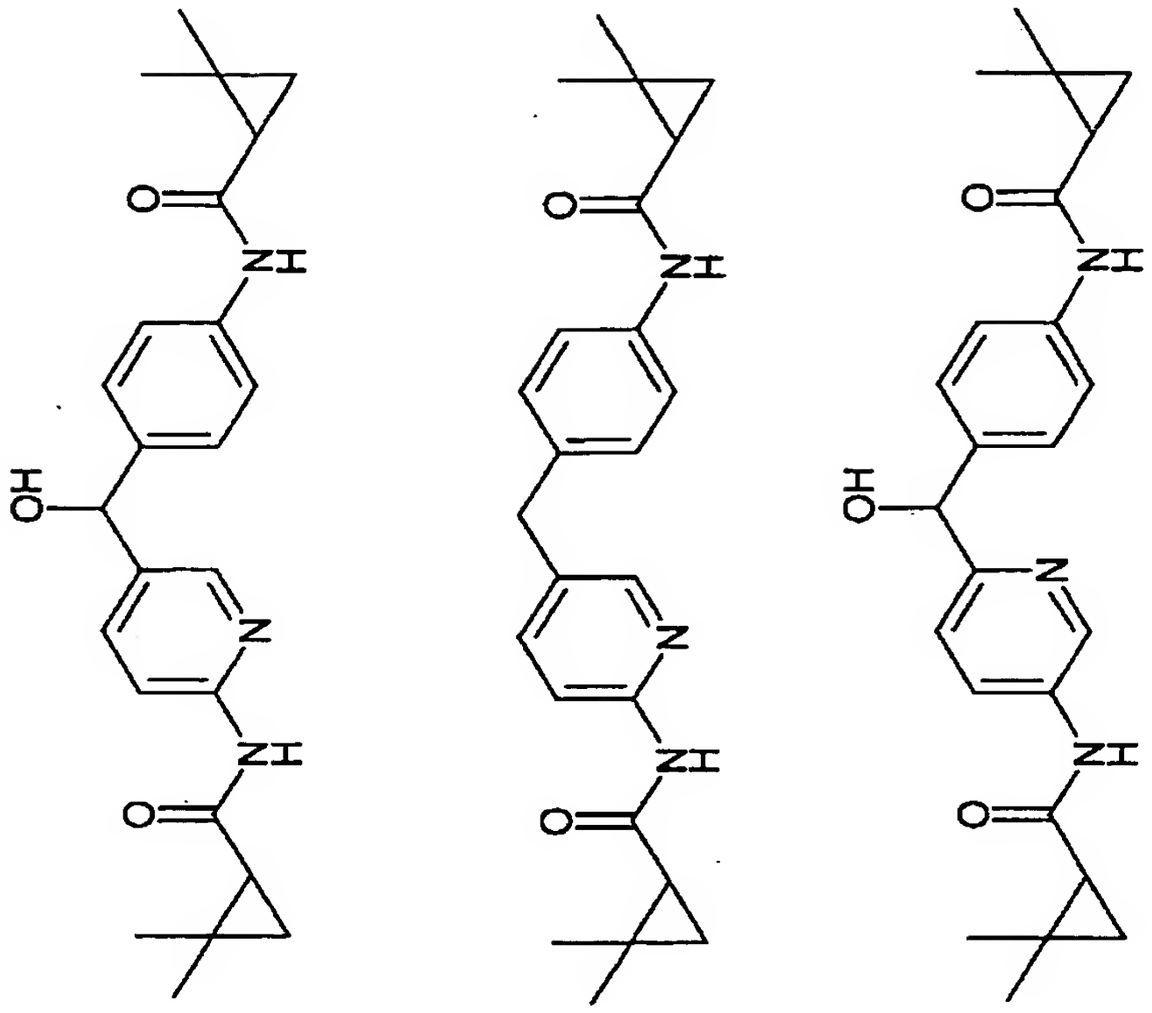
Further, in the present invention, R^{1} and R^{4} may be the same or different from each other, which may be either of a 2,2-dimethylcyclopropyl group, a 2,2-dichlorocyclopropyl group, a 2,2-difluorocyclopropyl group or a 2,2-dibromocyclopropyl group, and preferably -Y- should be -CO- and n = 0.

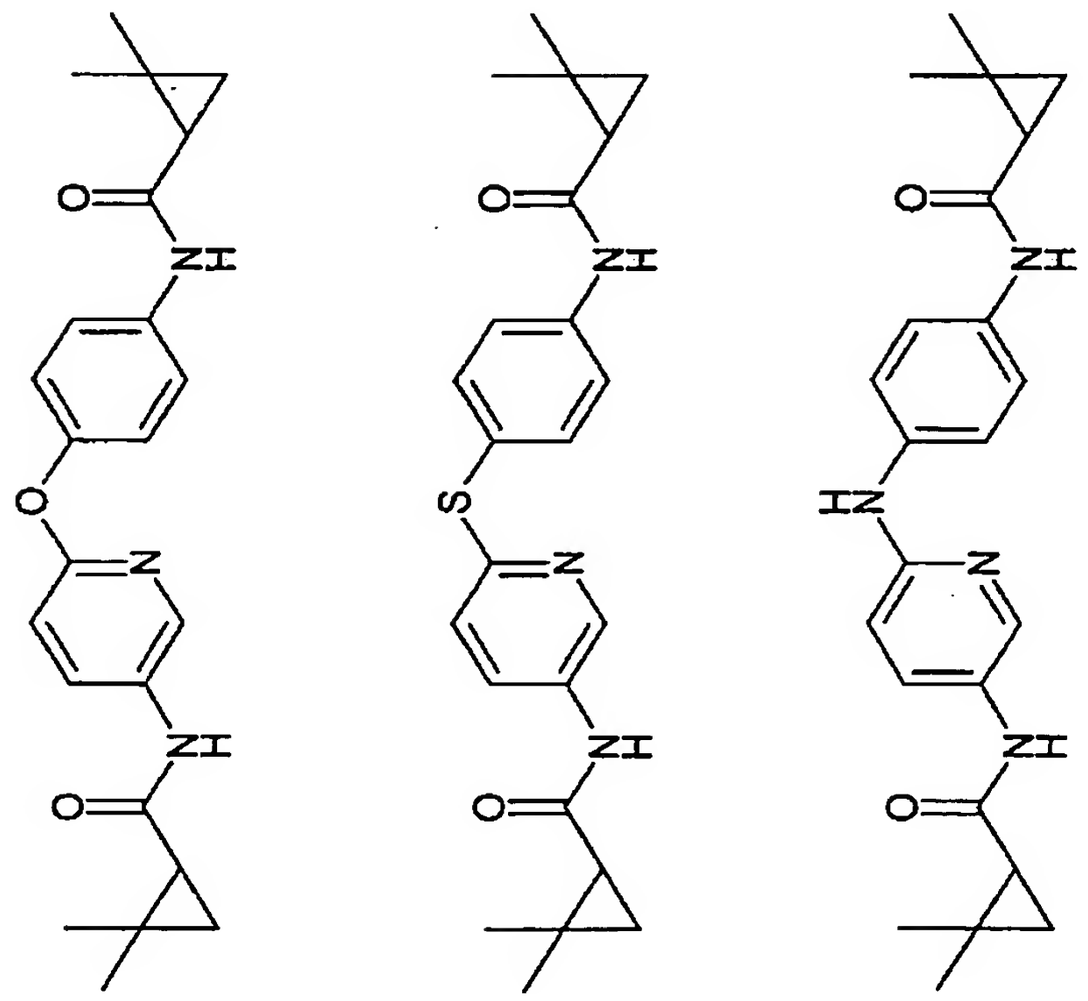
Further in the present invention, preferably R^{1} should be either of a 2,2-dimethylcyclopropyl group, a 2,2-dichlorocyclopropyl group, a 2,2-difluorocyclopropyl group or a 2,2-dibromocyclopropyl group; R^{4} should be an aryl

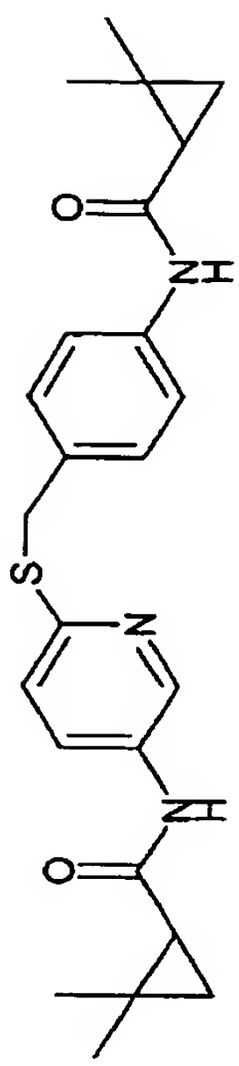
group or an aryl group having a substituent(s); -Y- should be the -CO-; and n should be an integer selected from 1 to 3.

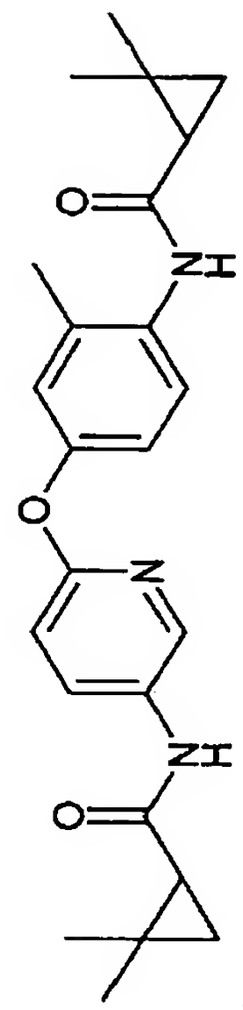
Further in the present invention, preferably R^1 should be either of a 2,2-dimethylcyclopropyl group, a 2,2-dichlorocyclopropyl group, a 2,2-difluorocyclopropyl group or a 2,2-dibromocyclopropyl group; R^4 should be an aryl group or an aryl group having a substituent(s); -Y- should be an interatomic bond, and n should be an integer selected from 2 to 4.

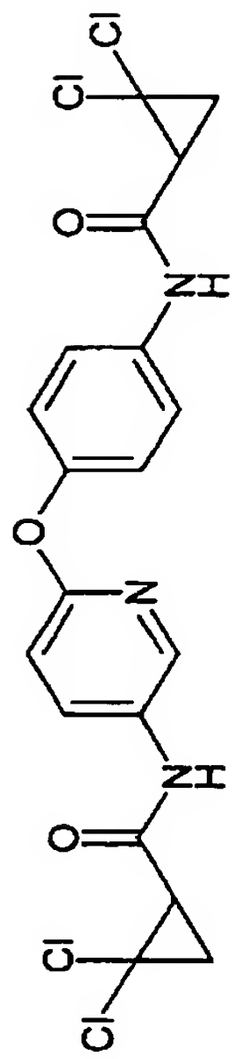
Further in the present invention, a heterocyclic compound or a pharmaceutically acceptable salt thereof represented by any of the following formulas is preferred.

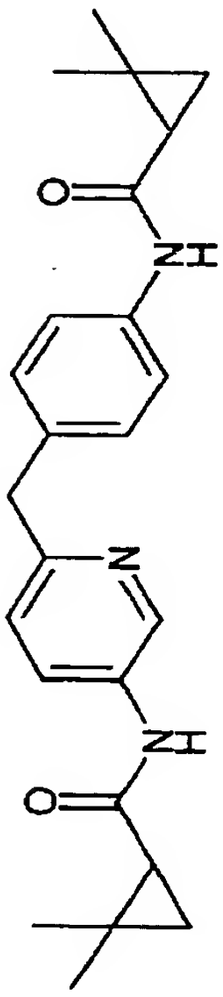


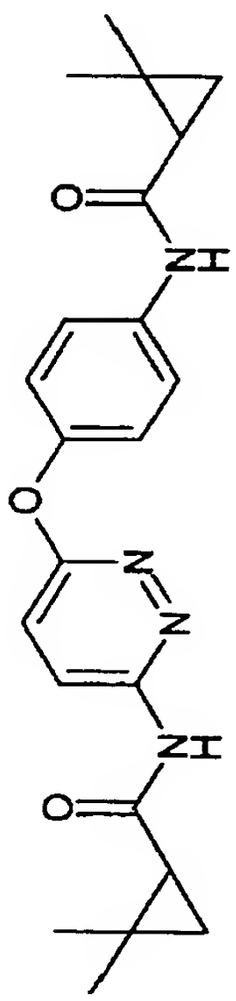


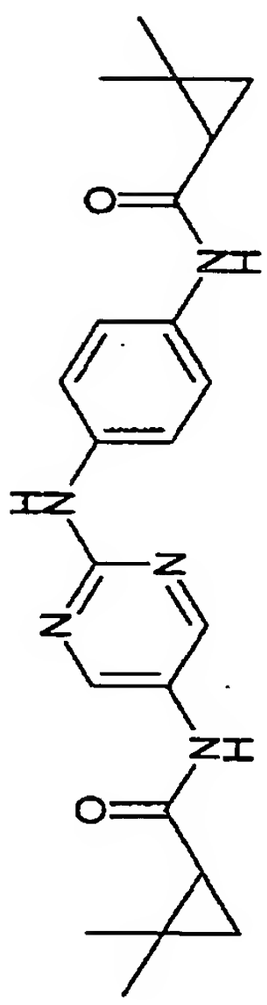


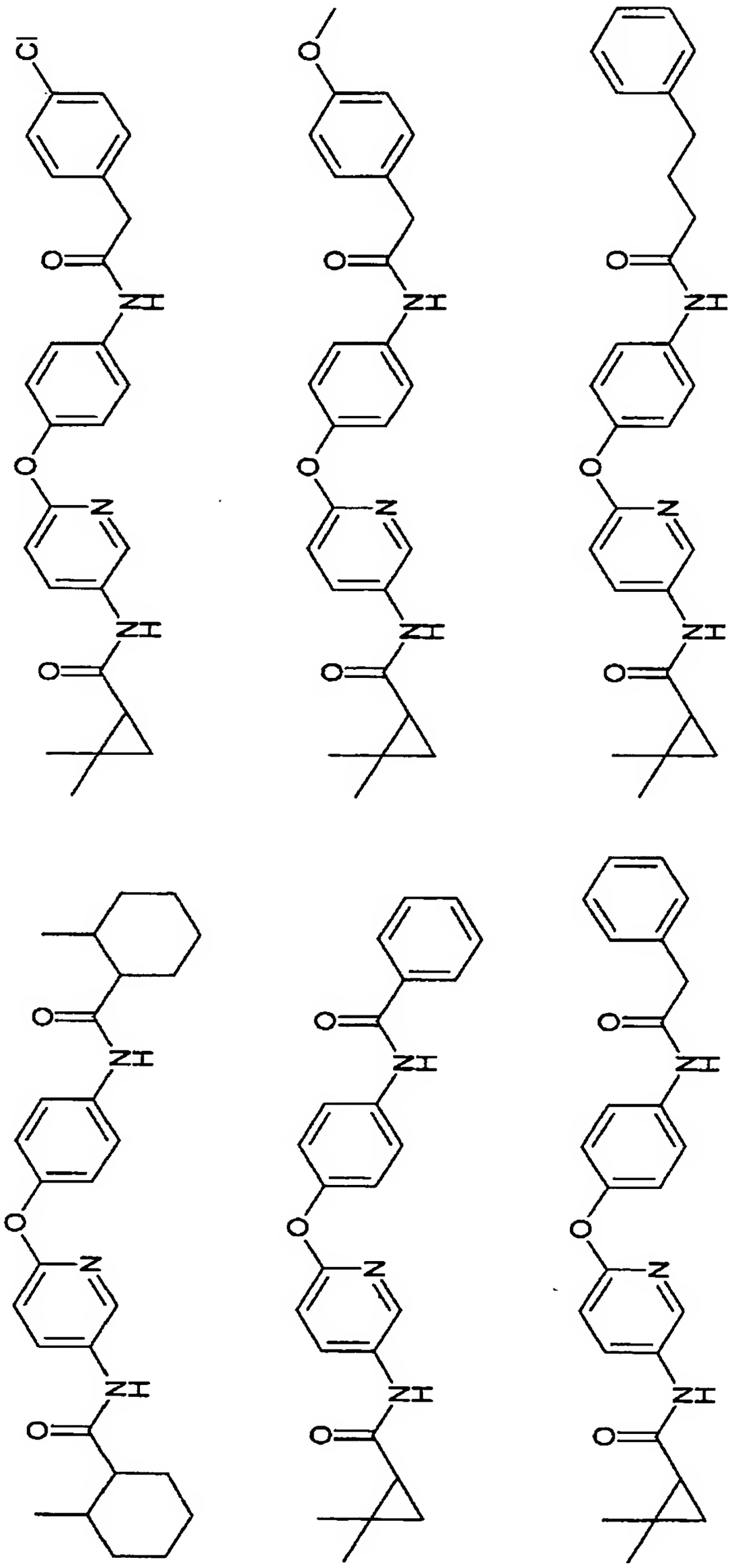


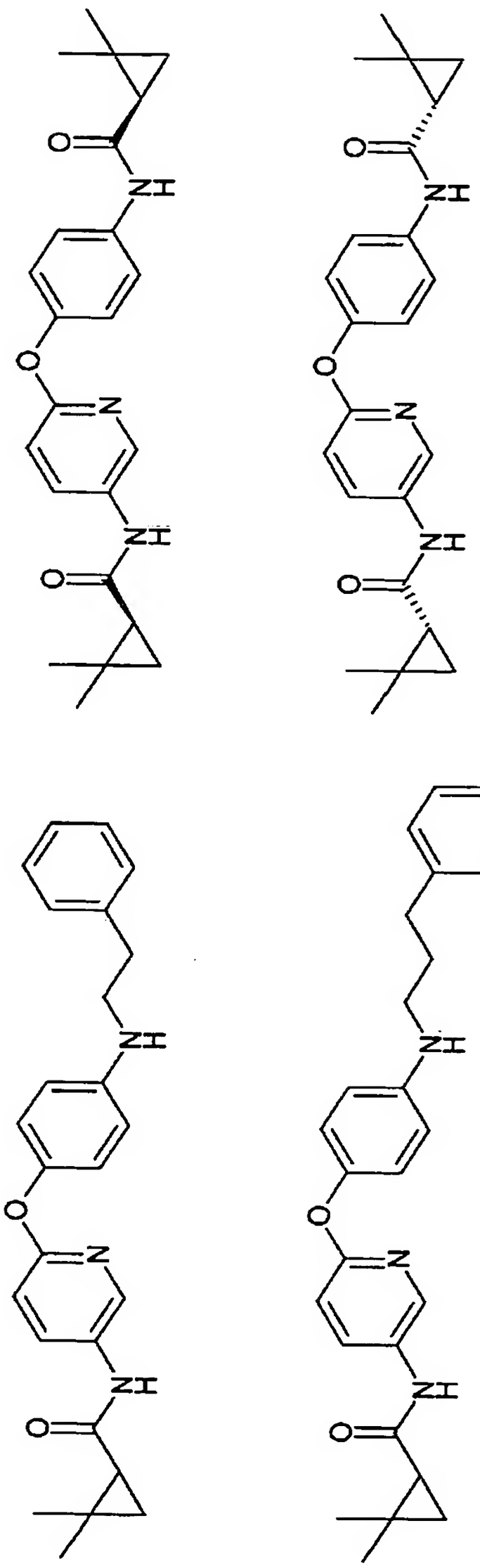


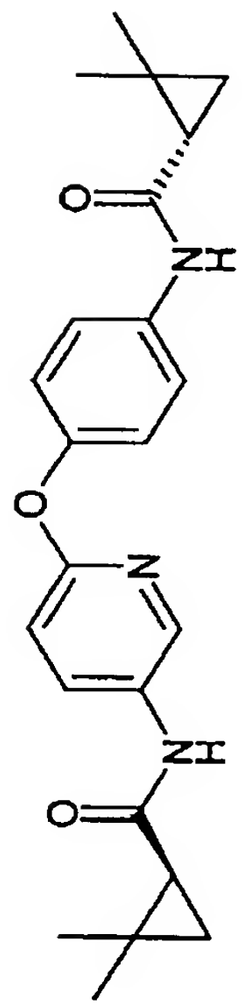












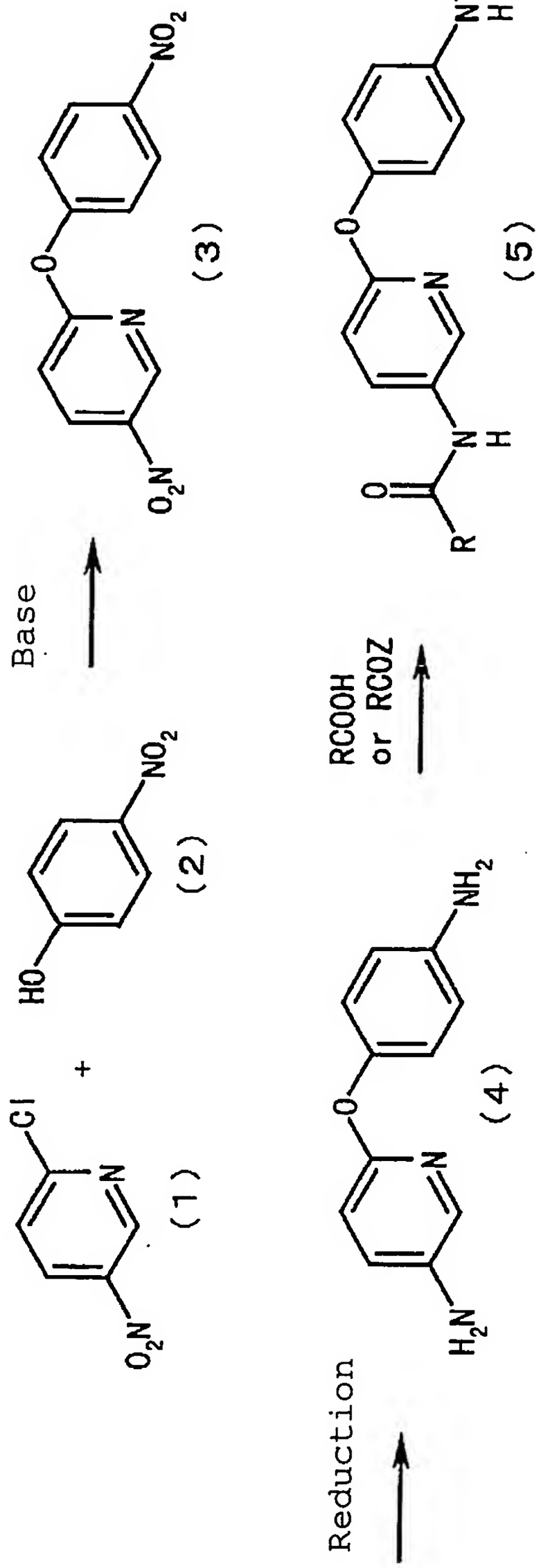
The pharmaceutically acceptable salt includes, for a sufficiently acidic compound according to the present invention, for example, an ammonium salt, an

alkali metal salt (for example, a sodium salt and a potassium salt which are preferable) and an alkali earth metal salt (for example, a calcium salt and a magnesium salt which are preferable) of the compound, and for a salt of organic bases, for example, a dicyclohexylamine salt, a benzathine salt, a N-methyl-D-glucan salt, a hydramine salt and a salt of amino acid such as arginine or lysine. Further, for a sufficiently basic compound according to the present invention, the pharmaceutically acceptable salt specifically includes an acid added salt of the compound, for example, an inorganic acid salt such as hydrochloric acid, sulfuric acid, nitric acid and phosphoric acid, or an organic acid salt such as acetic acid, lactic acid, citric acid, tartaric acid, maleic acid, fumaric acid and monomethylsulfate. Further, depending on the case, the salt may includes a salt hydrate or a hydrate.

It is to be noted that the present invention should include all of the isomers such as an optical isomer and a geometric isomer, a hydrate, a solvate or a crystal form.

The compounds of the present invention can be synthesized by way of the following method.

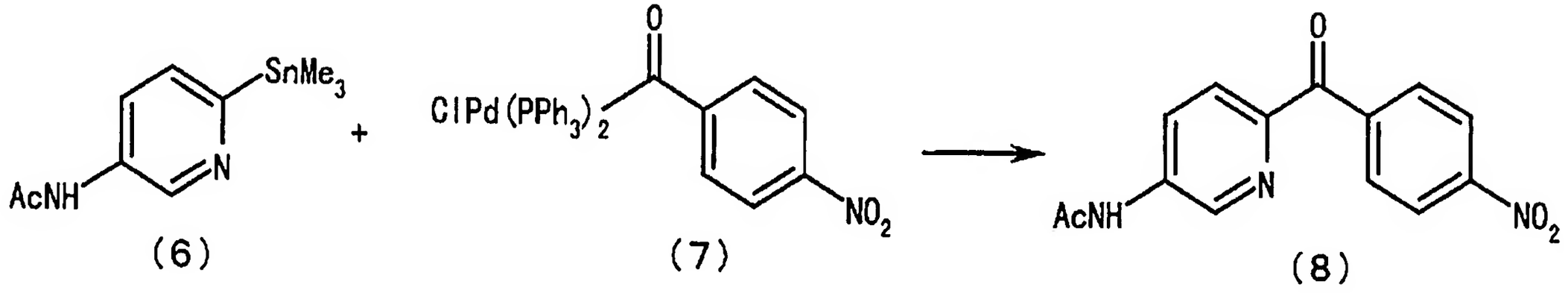
For example, compounds of the present invention defined in (I) wherein X is an oxygen atom, Y is a carbonyl group, n=0, A is pyridine, B is benzene and R^1 and R^4 are the same, can be obtained by reacting corresponding diamine compounds with corresponding acid halide such as an acid chloride by 2 or more equivalents in the presence of base, or otherwise may be reacted with carboxylic acid by 2 or more equivalents in the presence of the condensation agent, as shown below, thereby obtaining the intended compound.



wherein R is a cycloalkyl group having a substituent(s) or a cycloalkenyl group having a substituent(s), and the Z is a halogen atom

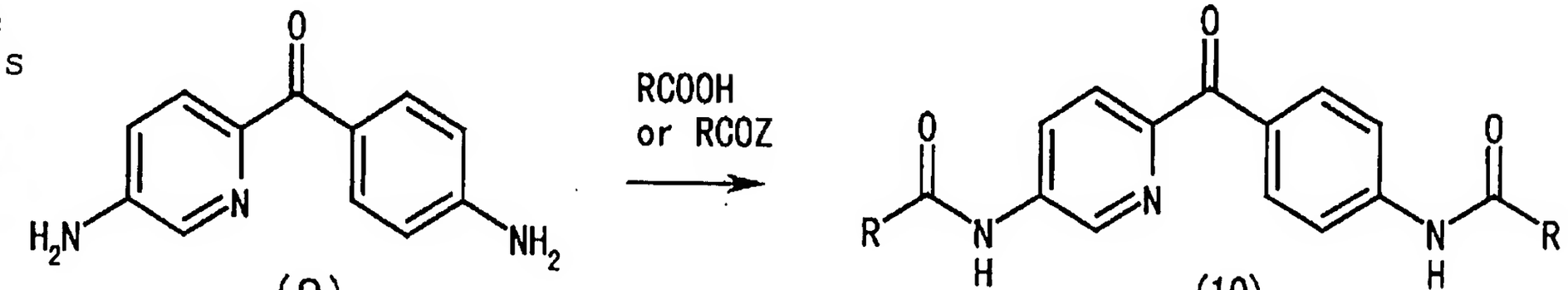
Further, by using the reaction shown above with small modification applied thereto, it will be also possible to synthesize a compound wherein X is a nitrogen atom or a sulfur atom, a compound wherein A is a heterocyclic ring other than pyridine, or a compound wherein B is an aromatic or a heterocyclic ring other than benzene ring.

For example, compounds of present invention defined in (I) wherein X is a carbon atom, Y is a carbonyl group, n=0, A is a pyridine, B is a benzene and R^1 and R^4 are the same, can be obtained by reacting corresponding diamine compounds with corresponding acid halide such as an acid chloride by 2 or more equivalents in the presence of base, or otherwise may be reacted with a carboxylic acid by 2 or more equivalents in the presence of a condensation agent, leading to a ketone body, which will be further reduced to an alcohol compound and the alcohol compound will be further reduced so as to synthesize a methylene body, as shown below.



(6) (7) (8)

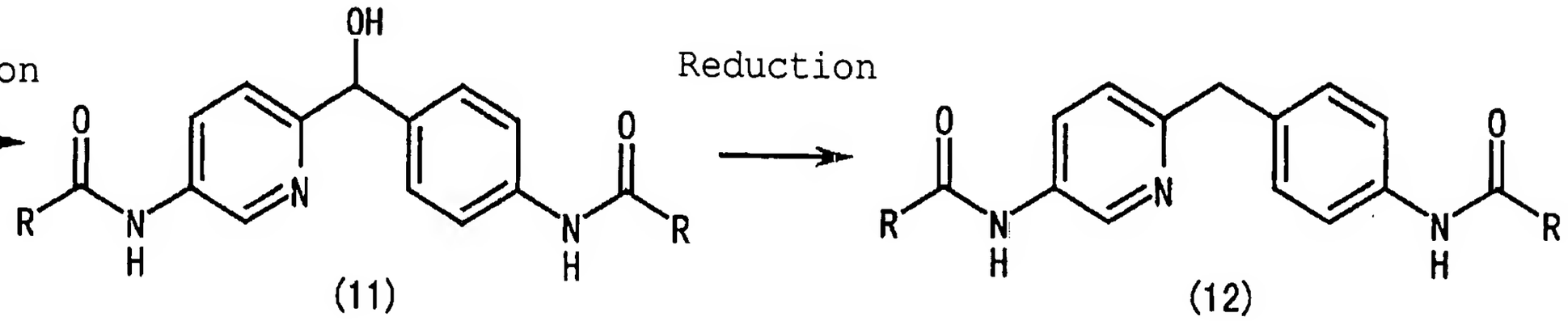
Reductive hydrolysis



(9) (10)

RCOOH or RCOZ

Reduction



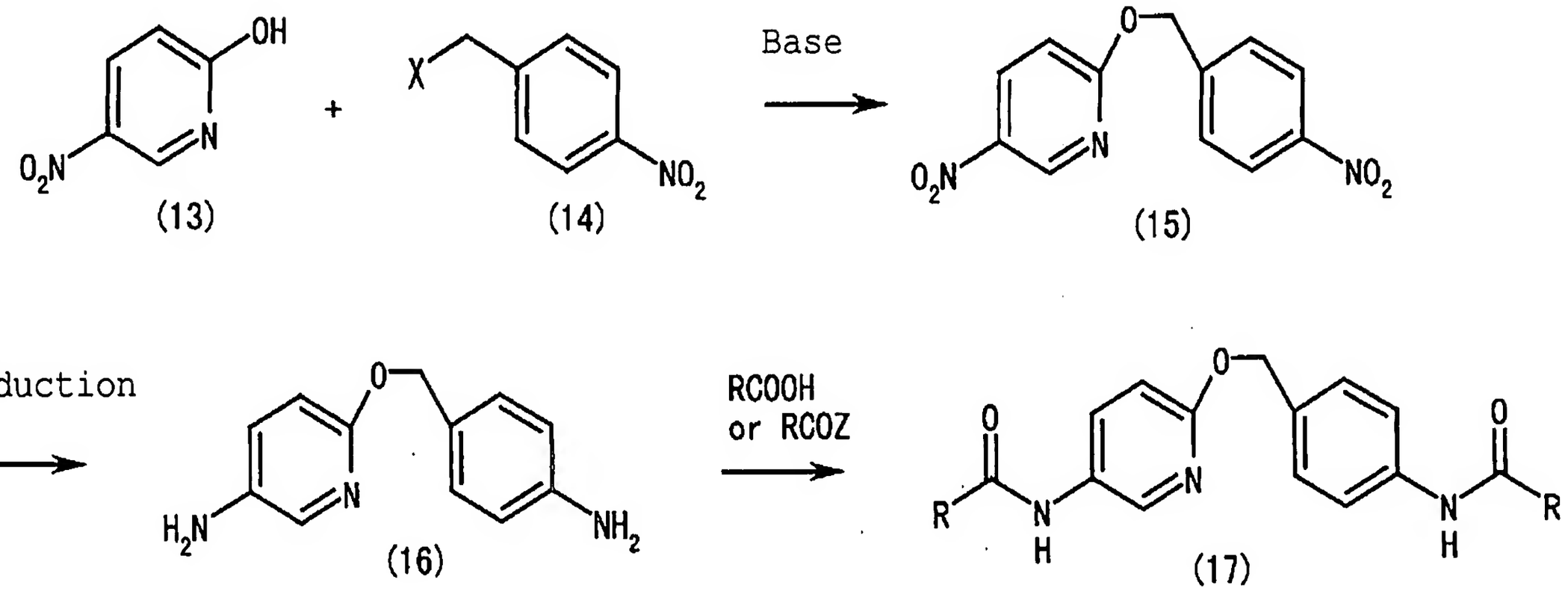
(11) (12)

Reduction

wherein R is a cycloalkyl group having a substituent(s) or a cycloalkenyl group having a substituent(s), and Z is a halogen atom.

Further, in the above reactions, a compound having different amide substituents at opposite ends can be synthesized by introducing sequentially the amide substituents by way of, for example, changing the sequence of the procedures after (XI) so that hydrolyzing may be practiced first to generate an amine compound, which will be precedently acylated.

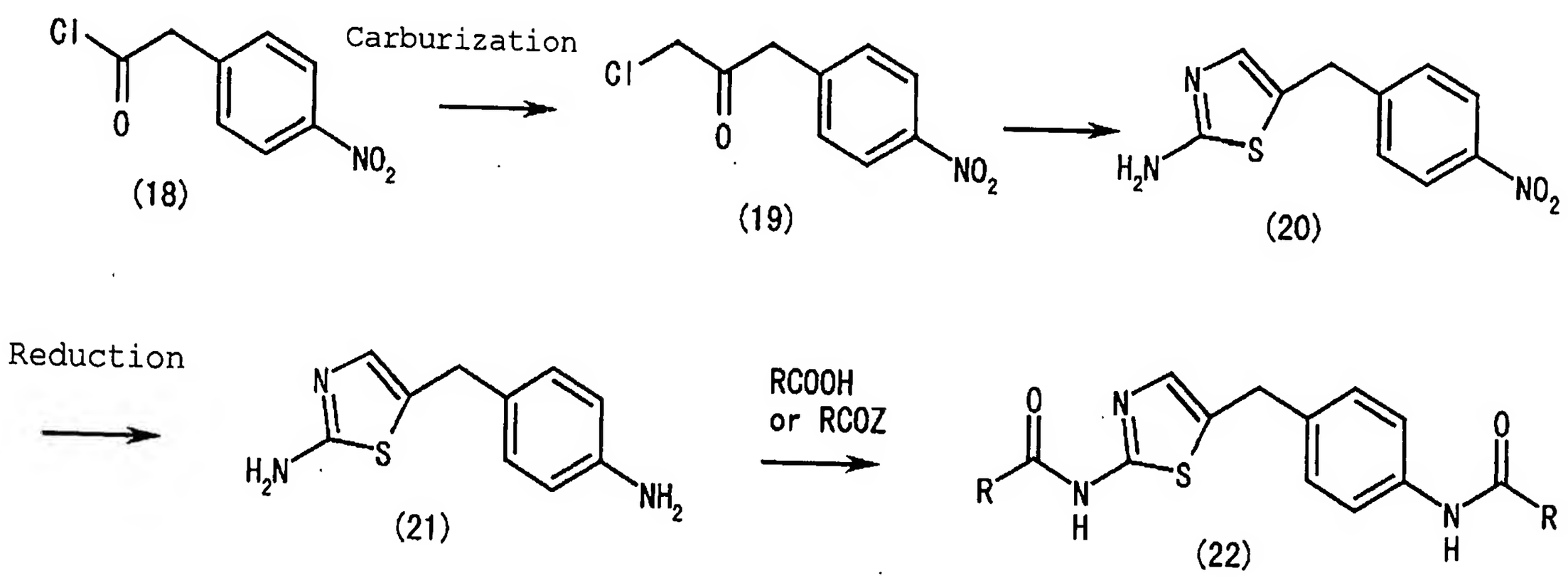
For example, compounds of the present invention defined in (I) wherein -X- is $-OCH_2-$, Y is a carbonyl group, n=0, A is pyridine, B is benzene, and R^1 and R^4 are the same, can be obtained by reacting corresponding diamine compounds with corresponding acid halide such as an acid chloride by 2 or more equivalents in the presence of base, or otherwise may be reacted with a carboxylic acid by 2 or more equivalents in the presence of a condensation agent, thereby obtaining the objective compound, as shown below.


OH
N
O_2N
(13)
+
X
NO_2
(14)
Base
O
N
O_2N
NO_2
(15)
Reduction
O
N
H_2N
NH_2
(16)
RCOOH
or RCOZ
O
N
R
N
H
O
R
(17)

wherein R is a cycloalkyl group having a substituent(s) or a cycloalkenyl group having a substituent(s), X is a leaving group such as a halogen atom and Z is a halogen atom.

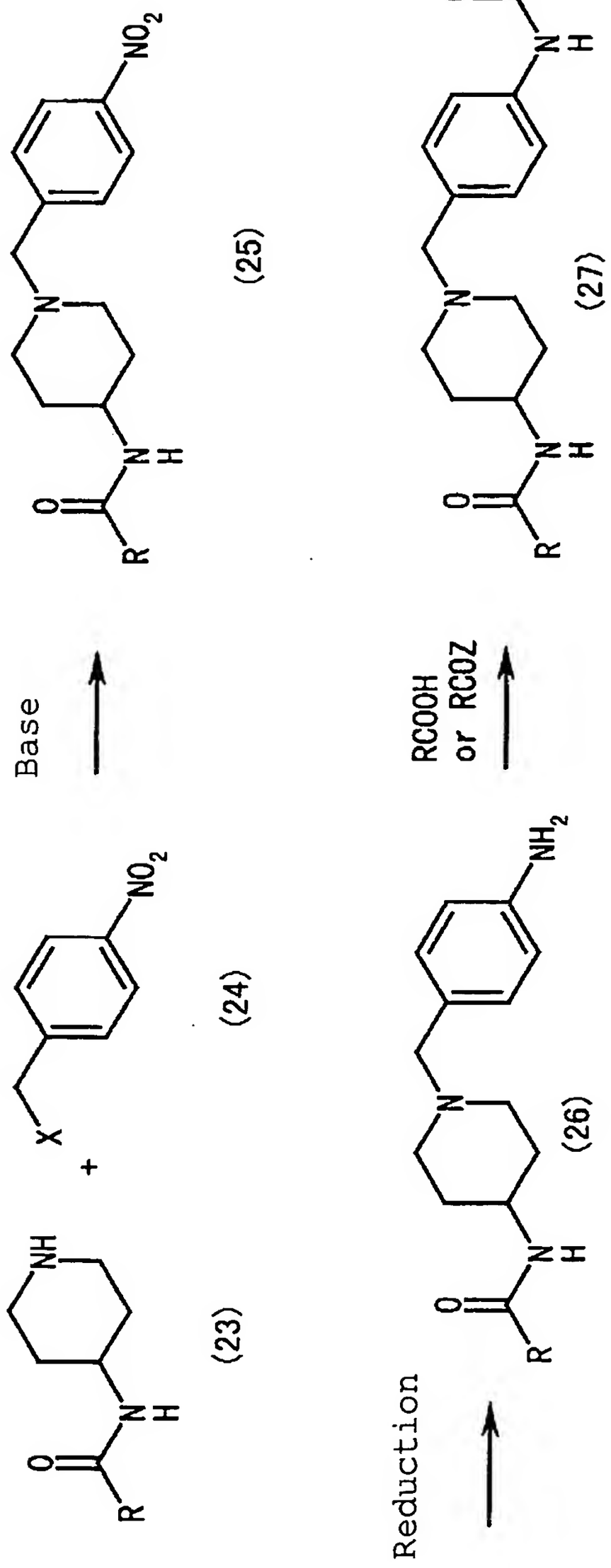
Further, by using the reaction shown above with small modification applied thereto, a compound wherein X is $-OCH_2CH_2CH_2-$ or $-SCH_2-$ can be synthesized

For example, compounds of the present invention defined in (I) wherein -X- is $-CH_2-$, Y is a carbonyl group, n=0, A is a thiazole, B is benzene, and R^1 and R^4 are the same, can be obtained by reacting corresponding diamine compounds with corresponding acid halide such as an acid chloride by 2 or more equivalents in the presence of base, or otherwise may be reacted with a carboxylic acid by 2 or more equivalents in the presence of the condensation agent, thereby obtaining the objective compound, as shown below.


Cl
O
NO2
(18)
Carburization
Cl
O
NO2
(19)
N
S
H2N
NO2
(20)
Reduction
N
S
H2N
NH2
(21)
RCOOH
or RCOZ
O
N
S
R
N
H
O
N
H
R
(22)

wherein R is a cycloalkyl group having a substituent(s) or a cycloalkenyl group having a substituent(s), and Z is a halogen atom.

For example, compounds of present invention defined in (I) wherein -X- is -CH_2-, Y is a carbonyl group, n=0, A is piperidine, B is benzene, and R^1 and R^4 are the same, can be obtained by reacting corresponding diamine compounds with corresponding acid halide such as an acid chloride by 2 or more equivalents in the presence of base, or otherwise may be reacted with a carboxylic acid by 2 or more equivalents in the presence of the condensation agent, thereby obtaining the objective compound, as shown below.

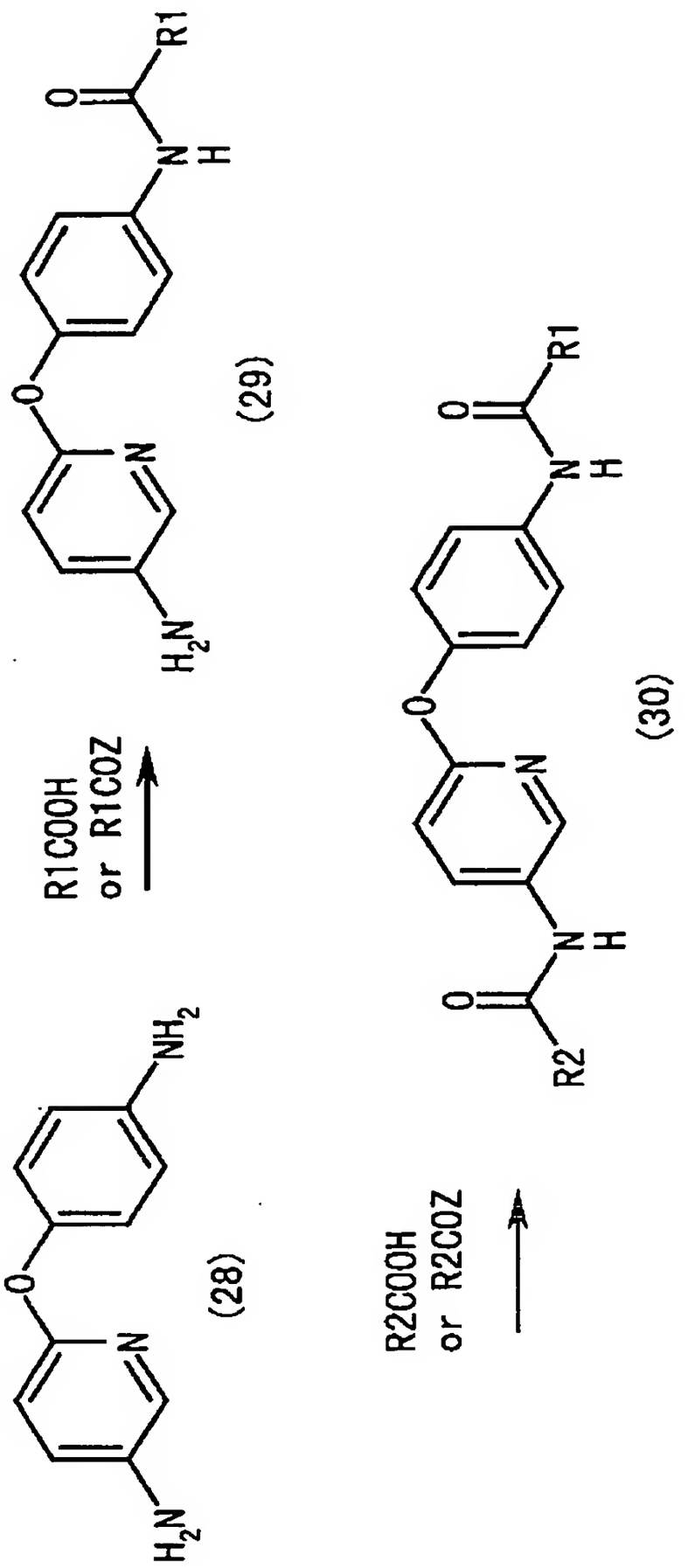


wherein R is a cycloalkyl group having a substituent(s) or a cycloalkenyl group having a substituent(s), X is a leaving group such as a halogen atom and Z is a

halogen atom.

Further, by using the reaction shown above with small modification applied thereto, a compound wherein X of $-CH_2CH_2-$ can be synthesized.

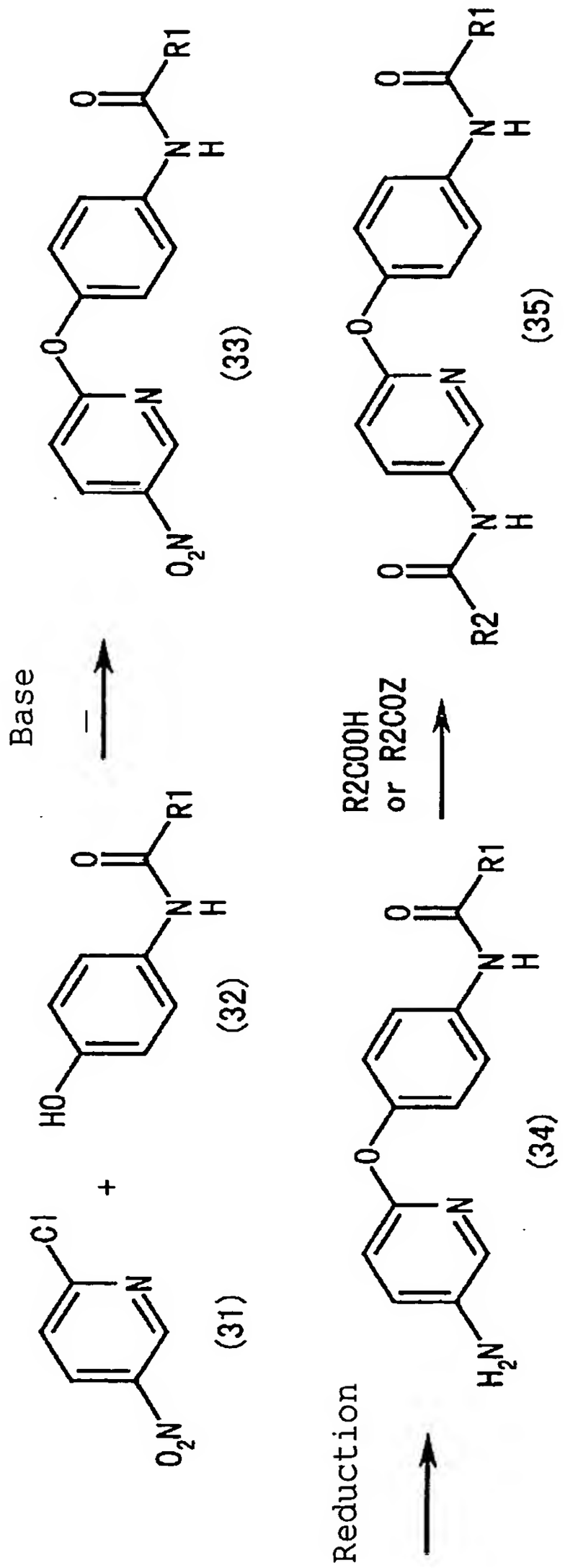
For example, compounds of the present invention defined in (I) wherein -X- is an oxygen atom, Y is a carbonyl group, n=0, A is pyridine, B is benzene, and R^1 and R^4 are different from each other, can be obtained by reacting, corresponding diamine compounds with corresponding acid halide such as an acid chloride by about one equivalent in the presence of base, or otherwise may be reacted with a carboxylic acid by about one equivalent in the presence of the condensation agent, thereby introducing a substituent(s) to one end of the diamine compound, and similarly the resultant compound may be additionally reacted with the acid halide or the carboxylic acid having a structure different from that of the acid halide or the carboxylic acid which has been used in the preceding stage so as to obtain the objective compound, as shown below.



wherein R1 is an alkyl group, an alkyl group having a substituent(s), a cycloalkyl group, a cycloalkyl group having a substituent(s), a cycloalkenyl group, a cycloalkenyl group having a substituent(s), an aryl group, an aryl group having a substituent(s), a heterocyclic ring having one or more hetero atoms or a heterocyclic ring having one or more hetero atoms and a substituent(s); R2 is a

cycloalkyl group having a substituent(s) or a cycloalkenyl group having a substituent(s); and Z is a halogen atom.

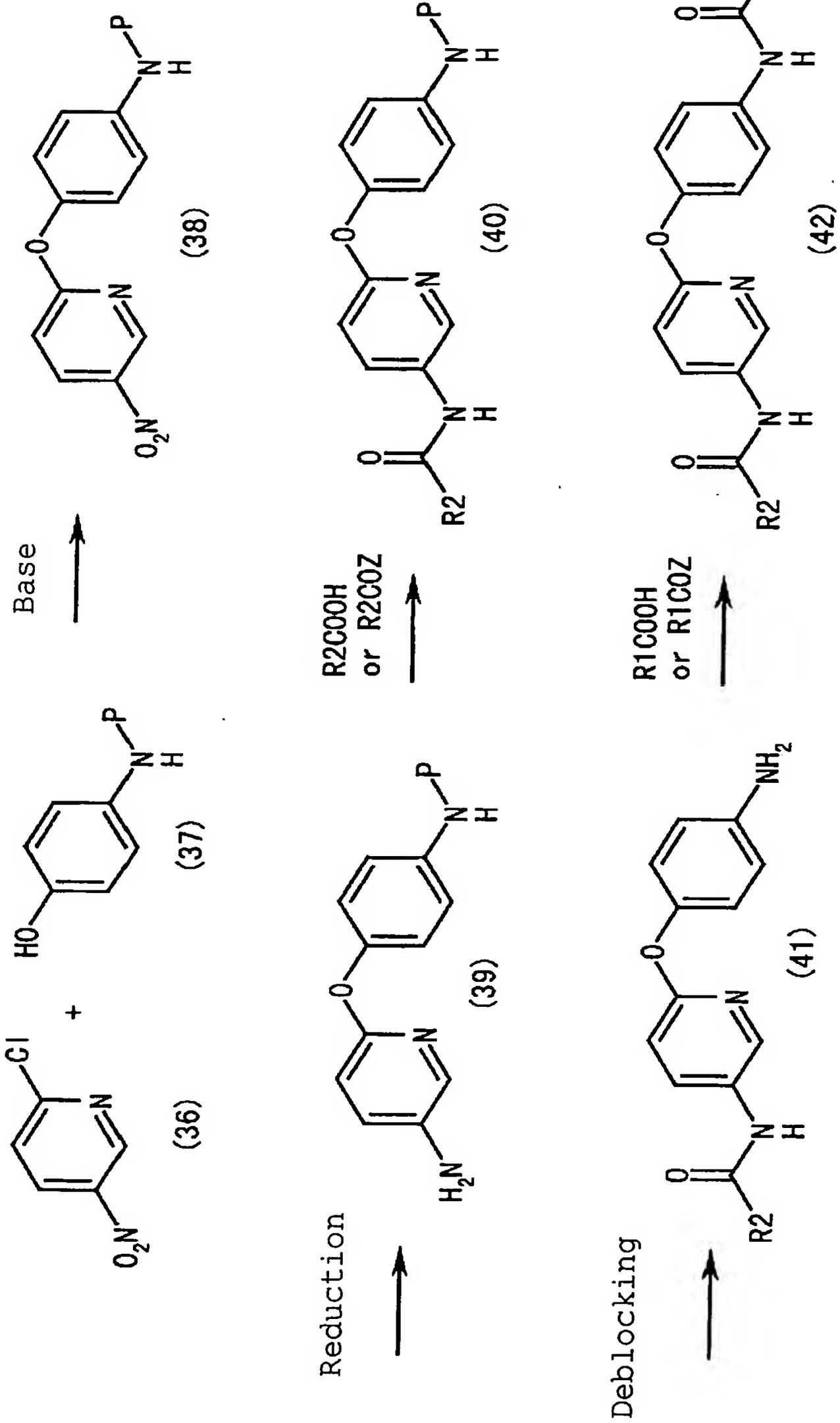
Further, a compound having R^1 different from R^4 can be synthesized by, for example, introducing an acyl group in incremental steps according to an alternative method as shown below.



wherein R1 is an alkyl group, an alkyl group having a substituent(s), a cycloalkyl group, a cycloalkyl group having a substituent(s), a cycloalkenyl group, a

cycloalkenyl group having a substituent(s), an aryl group, an aryl group having a substituent(s), a heterocyclic ring having one or more hetero atoms or a heterocyclic ring having one or more hetero atoms and a substituent(s); R2 is a cycloalkyl group having a substituent(s) or a cycloalkenyl group having a substituent(s); and Z is a halogen atom.

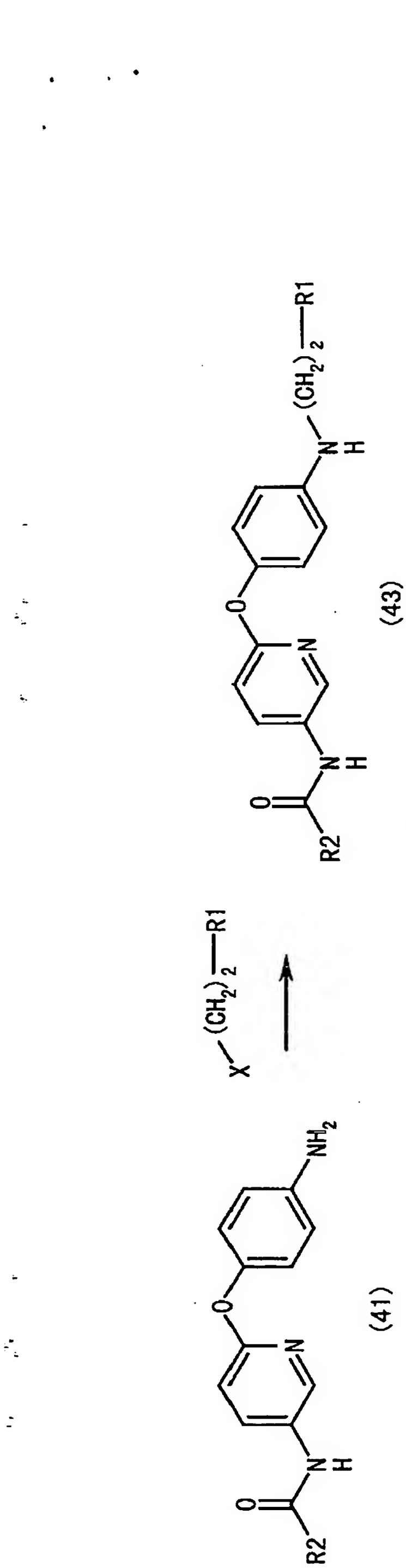
Further, a compound having R^1 different from R^4 can be synthesized also using such a method in which a substituent(s) for R1 may be introduced at the last stage by elaborating an amine protector as an intermediate, as shown below.



wherein R1 is an alkyl group, an alkyl group having a substituent(s), a cycloalkyl group, a cycloalkyl group having a substituent(s), a cycloalkenyl group, a

cycloalkenyl group having a substituent(s), an aryl group, an aryl group having a substituent(s), a heterocyclic ring having one or more hetero atoms or a heterocyclic ring having one or more hetero atoms and a substituent(s); R2 is a cycloalkyl group having a substituent(s) or a cycloalkenyl group having a substituent(s); Z is a halogen atom; and P is an amino protective group.

For example, compounds of the present invention defined in (I) wherein X is an oxygen atom, Y is an interatomic bond, n=2, A is a pyridine and B is a benzene, can be obtained by reacting monoamide compounds with corresponding alkylating agent such as an alkyl halide in the presence of base, as shown below, thereby obtaining the objective compound.



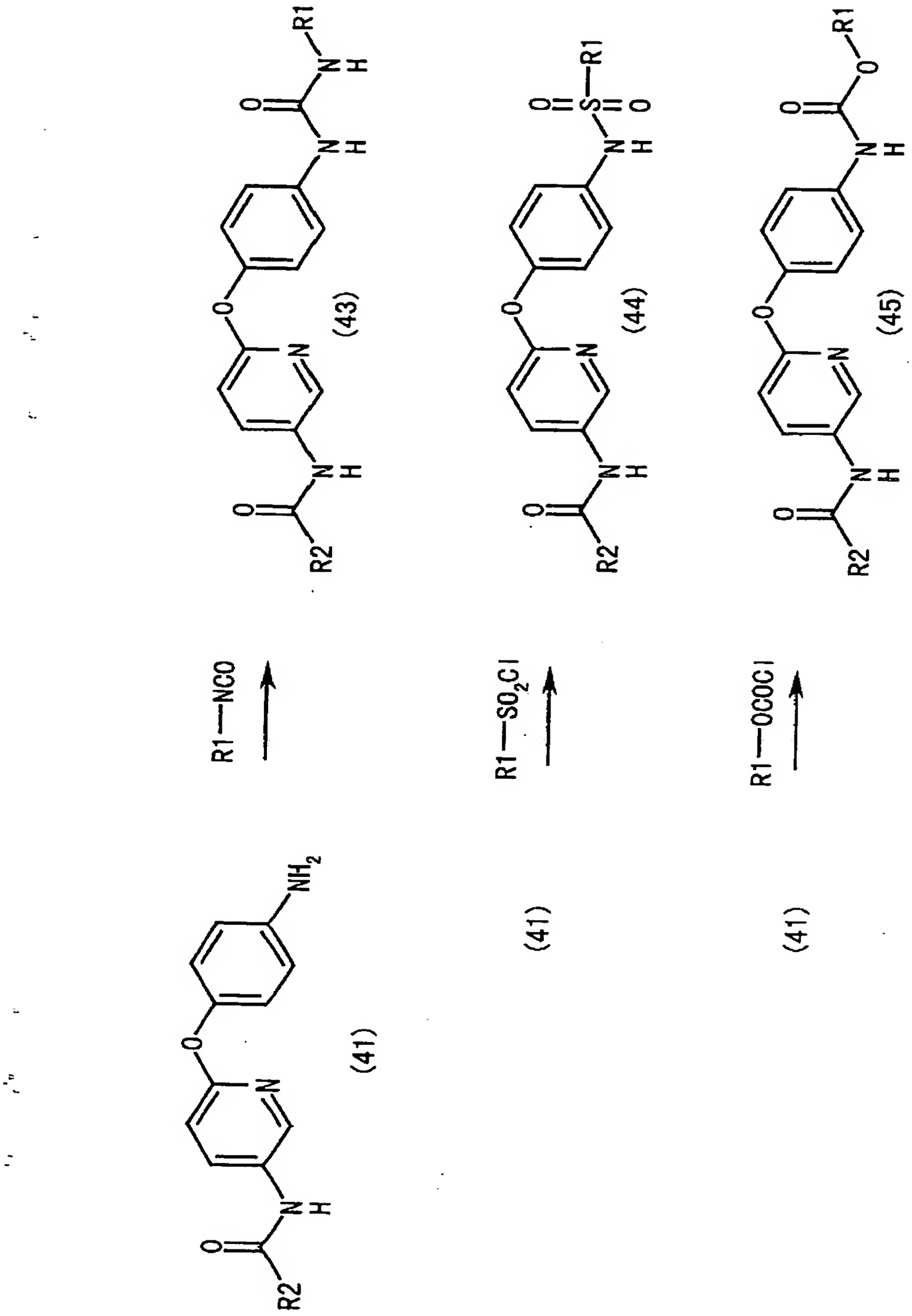
(41)

(43)

wherein R1 is an alkyl group, an alkyl group having a substituent(s), a cycloalkyl

group, a cycloalkyl group having a substituent(s), a cycloalkenyl group, a cycloalkenyl group having a substituent(s), an aryl group, an aryl group having a substituent(s), a heterocyclic ring having one or more hetero atoms, or a heterocyclic ring having one or more hetero atoms and a substituent(s); and R2 is a cycloalkyl group having a substituent(s) or a cycloalkenyl group having a substituent(s).

To synthesize, for example, the compounds of the present invention defined in (I) wherein X is an oxygen atom, -Y- is -CONH-, -SO_2- or -COO-, n=0, A is a pyridine and B is a benzene, for example, monoamide compounds may be used as a starting material, and then they may be reacted respectively with the corresponding isocyanate, sulfonyl halide, or ester chlorocarbonate, as shown below, thereby obtaining the objective compound.



wherein R1 is an alkyl group, an alkyl group having a substituent(s), a cycloalkyl group, a cycloalkyl group having a substituent(s), a cycloalkenyl group, a

cycloalkenyl group having a substituent(s), an aryl group, an aryl group having a substituent(s), a heterocyclic ring having one or more hetero atoms, or a heterocyclic ring having one or more hetero atoms and a substituent(s); and R2 is a cycloalkyl group having a substituent(s) or a cycloalkenyl group having a substituent(s).

Further, by using a reaction similar to the aforementioned reaction, a compound having -Y- of -CSNH- or -SO- may be synthesized.

It should be appreciated that those compounds of the present invention obtainable by the methods defined above can be refined by using the known technologies, including the extraction, distillation, crystallization or column chromatography, which have been normally used in the organic synthesis.

Those obtained compounds of the present invention, as will be described later, have an activity for inhibiting the AP-1 or NF-kappaB activation and thus are useful in providing the cure against the inflammatory diseases which might be developed by those transcription factors. That is, the compounds of the present invention are useful as an anti-inflammatory agent, an anti-rheumatism agent, an immunosuppressive agent, a cancer metastasis inhibitor, an antiviral agent or a curative agent for arterial sclerosis, advantageously without side effects such as hormone action, which can inhibit the transcription of genes of a plurality of inflammatory cytokines, matrix metalloproteases, inflammatory cell adhesion factors, and so on.

If the compound of the present invention is used as a drug such as the anti-inflammatory agent, it may be administered in the manners of an oral administration, an intravenous administration, a percutaneous administration and an administration by way of eye-instillation. A dosage should be different depending on the symptom, an age of a patient and the applied administration

The compound of the present invention can be formulated by the conventional method. The compound can be formulated as a drug product in the forms of, for example, an injection, a tablet, a granule, a fine granule, a powder, a capsule, a cream, a suppository and the like, wherein those formulation carriers are available for the drug product, including, for example, lactose, glucose, D-mannitol, starch, crystalline cellulose, calcium carbonate, kaolin, amylum, gelatin, hydroxypropylcellulose, hydroxypropylmethylcellulose, polyvinyl pyrrolidone, ethanol, carboxymethylcellulose, carboxymethyl cellulose calcium salt, magnesium stearate, talc, acetyl cellulose, saccharose, titanium oxide, benzoic acid, p-oxybenzoate ester, sodium dehydro acetate, gum arabic, tragacanth, methylcellulose, egg york, surfactant, sucrose, simple syrup, citric acid, distilled water, ethanol, glycerin, propylene glycol, macrogol, sodium monohydrogen phosphate, sodium dihydrogen phosphate, sodium phosphate, dextrose, sodium chloride, phenol, thimerosal, p-oxybenzoic ester and sodium hydrogensulfite, which will be mixed with the compound of the present invention in use depending on the form of the drug product.

Further, a content of an active constituent included in the drug product of the present invention may be varied in dependence on the form of the drug product and not specifically limited but typically in the range of 0.01~100 weight percent, preferably in the range of 1~100 weight percent.

The present invention will now be described in more detail with reference to examples, though the present invention is not limited to those.

(Example 1)

Process 1: Synthesis of a diamine compound (4)

Potassium carbonate (55.2g, 0.4mol) was added into dimethylformamide (300ml) solution including 2-chloro-5-nitropyridine (1) (31.7g, 0.2mmol) and 4-

been completed, the solution was poured into water (1.5 liter), and the separated-out solid was filtered and dried, thereby obtained a dinitro compound (3) (48.2g, 92%). The obtained dinitro compound (3) (26.1g, 0.1mol) was dissolved into methanol (1.75 liter), into which in turn 10% palladium carbon (50% water content) (2.61g) was added, and further hydrogen gas was blown, thus reduced under normal pressure. After the reaction having been completed, celite filtering was applied to remove the palladium carbon, and then, after the solvent having been evaporated, it was purified by using silica gel column chromatography (dichloromethane, methanol), thus obtained a diamine compound (4) (15.8g, 79%).

1H-NMR (300MHz,$CDCl_3$) δ =6.67 (2H, d, J=8.7Hz), 6.68 (1H, d, J=8.7Hz), 6.89 (2H, d, J=8.7Hz), 7.04 (1H, dd, J=8.7, 3.0Hz), 7.69 (1H, d, J=3.0Hz).

MS(ESI) m/z 202$(M+H)^+$.

Process 2: Synthesis of a compound of example 1 (5:R=2,2-dimethylcyclopropane)

The diamine compound (4) (2.035g, 10mmol) obtained in the process 1 was dissolved in dichloromethane (100ml) and added with triethylamine (4ml, 29mmol) and 2,2-dimethylcyclopropanecarbonyl chloride (3.37g, 25mmol), which in turn was stirred at room temperature for 14 hours. After the reaction having been completed, the solvent was evaporated, and then extracted with ethyl acetate followed by washing, drying and concentration according to the conventional manner applied to the resultant, which was further purified by using silica gel column chromatography (ethyl acetate, hexane), thus obtained an objective compound of example 1 (2.77g, 70%).

1H-NMR (300MHz, DMSO-d6), δ =0.75-0.82 (2H, m), 0.96-1.01 (2H, m), 1.13-1.18 (12H, m), 1.61-1.68 (2H, m), 6.93 (1H, d, J=8.7Hz), 7.00 (2H, d, J=8.7), 7.60 (2H, d, J=8.7Hz), 8.05 (1H, dd, J=8.7, 2.7Hz), 8,31 (1H, d, J=2.7Hz), 10.07 (1H, s), 10.22 (1H, s). MS(ESI) m/z 394$(M+H)^+$.

(Example 2)

According to the same method as in example 1, a compound of example 2 was synthesized by using 4-nitrobenzenethiol and 2-chloro-5-nitropyridine as the starting materials.

1H-NMR (300MHz, $CDCl_3$), δ =0.82-0.86 (2H, m), 1.17-1.26 (14H, m), 1.41-1.45 (2H, m), 6,87 (1H, d, J=8.7Hz), 7.44 (2H, d, J=8.7Hz), 7.52-7.55 (2H, m), 7.78-7.81 (2H, m), 7.86-7.88 (1H, m), 8.37 (1H, d, J=2.4Hz). MS(ESI) m/z 410$(M+H)^+$.

(Example 3)

Triethylamine (35ml) was added into dimethylformamide (50ml) including 2-chloro-5-nitropyridine (1) (9.5g, 60mmol) and para-phenylenediamine hydrochloride (10.9g, 60mmol), and stirred at the room temperature for 14 hours. After the reaction having been completed, the solution was poured into water, and the resultant solid was filtered and then N-(5-nitropyridin-2-yl) para-phenylenediamine was obtained as a brown solid. This solid was dissolved in ethanol (800ml) and added with 5%-palladium carbon (2g) so as to cause a hydrogen substitution, and then reduced at 70℃ under the normal pressure for 6 hours. After the reaction having been completed, the celite filtering was applied to remove the palladium carbon, and then it was washed by using a mixed solvent of ethyl acetate and hexane, thus obtained N-(5-amino-pyridin-2-yl) para-phenylenediamine (8.8g, 75%).

Thereafter, according to the same method as of the process 2 in example 1, a compound of example 3 was obtained by using obtained diamine as the starting material.

1H-NHR (300MHz, DMSO-d6) δ =0.70-0.80(2H, m), 0.93-0.99 (2H, m), 1.15 (12H, s), 1.58-1.66 (2H, m), 6.74 (1H, d, J=9.0Hz), 7.44 (2H, d, J=9.0Hz), 7.50 (2H, d, J=9.0Hz), 7.77 (1H, dd, J=9.0, 2.7Hz), 8.28 (1H, d, J=2.7Hz), 8.77 (1H, s), 9.86 (1H, s), 9.92 (1H, s). MS(ESI) m/z 393$(M+H)^+$.

(Example 4)

Process 1: Synthesis of 2-acetamide-5-trimethylstannylpyridine (6)

Triethylamine (1ml, 7.2mmol), acetic anhydride (0.6ml, 6.35mmol) and 4-dimethylaminopyridine (1mg) were added into a dichloromethane (50ml) solution of 2-amino-5-bromopyridine (1g, 5.8mmol) and stirred at the room temperature for 15 hours. After the reaction having been completed, the solvent was evaporated and the resultant solution was made acidic by hydrochloric acid, and then the resultant was extracted with ethyl acetate, washed, dried and concentrated according to the conventional manner, thus obtained 2-acetamide-5-bromopyridine (808mg, 65%) as a white crystal. A toluene (3ml) solution of this 2-acetamide-5-bromopyridine (30mg, 0.14mmol), hexamethylditin (110mg, 0.336mmol) and tetrakis (triphenylphosphine) palladium (10mg, 0.01mmol) was stirred at 100℃ under argon for 18 hours. After the reaction having been completed, the solid matter was filtered out, and the filtrate was extracted with ethyl acetate, and then after having been washed, dried and concentrated according to the conventional manner, it was purified by using the silica gel thin-layer chromatography (the ethyl acetate, hexane), thus obtained 2-acetamide-5 -trimethylstannylpyridine (6) (10mg, 23%).

1H-NMR (300MHz, $CDCl_3$) δ =0.32 (9H, s), 2.20 (3H, s), 7.77 (1H, dd, J=8.1, 1.5Hz), 8.14 (1H, d, J=8.1Hz), 8.25 (1H, d, J=1.5Hz). MS(ESI) m/z 301$(M+H)^+$.

Process 2: Synthesis of a palladium complex (7)

A benzene (50ml) solution of 4-nitrobenzoyl chloride (926mg, 5mmol) and tetrakis (triphenylphosphine) palladium (2.89g, 2.5mmol) was stirred at the room temperature for 6 hours. After the completion of the reaction, the solvent was distilled out, and then the solution was washed by the ether thus obtained the palladium complex (7) in the form of a light orange crystal (2.08g).

1H-NMR (300MHz, $CDCl_3$), δ =7.21-7.39 (18H, m), 7.59-7.71 (14H, m), 7.80 (2H, d,

J=9.0Hz).

Process 3: Synthesis of example 4 compound (11:R=2,3-dimethylcyclopropane)

A toluene (20ml) solution of the 2-acetamide-5 -trimethylstannylpyridine (6) (100mg, 0.336mmol) obtained in the process 1 and the palladium complex (7) (390mg, 0.48mmol) obtained in the process 2 was stirred at 100℃ under argon for 2 hours. After the completion of the reaction, the solution was poured into diluted hydrochloric acid, extracted with ethyl acetate, and after having been washed, dried and concentrated according to the conventional manner, then purified by using silica gel chromatography (ethyl acetate, hexane), thus obtained objective material of 2-acetamide-5-(4-nitrophenylcarbonyl) pyridine (8) in the form of a light yellow crystal (18mg, 20%).

The obtained 2-acetamide-5-(4-nitrophenylcarbonyl) pyridine (8) (18mg, 0.063mmol) and $FeSO_4 \cdot 7H_2O$(200mg, 0.72mmol) were heated and refluxed for 10 minutes in the mixed solvent of water (4ml) and ethanol (0.5ml). Further, 100 mg of aquous ammonia solution was added thereto and reflux was continued for another 20 minutes. After the reaction having been completed, the solid matter was filtered out, and the filtrate was extracted with ethyl acetate and then washed, dried and concentrated according to the conventional manner, thus obtained 2-acetamide -5-(4-aminophenylcarbonyl) pyridine in the form of a yellow oily matter (11mg).

The obtained 2-acetamide-5-(4-aminophenylcarbonyl) pyridine (20mg) was stirred at 70℃ in 4M hydrochloric acid (3ml) for 2 hours. After the reaction was completed, the resultant was extracted with ethyl acetate, and then washed, dried and concentrated according to the conventional manner, purified by using silica gel thin-layer chromatography (ethyl acetate), thus obtained 2-amino-5-(4-aminophenylcarbonyl) pyridine (9) (5mg) in the form of a light yellow crystal.

4-dimethylaminopyridine (0.5mg) and 2,2-dimethylcyclopropane-carbonyl chloride (28mg, 0.2mmol) was added to a pyridine (3ml) solution of the obtained 2-amino-5-(4-amino-phenylcarbonyl) pyridine (9) (5mg, 0.022mmol), and stirred at the room temperature for 3 hours. After the completion of the reaction, the solution was extracted with ethyl acetate, and then washed, dried and concentrated according to the conventional manner, thus obtained a diamide compound (10:R= 2,2-dimethylcyclopropane) in the form of a yellow oily matter (15mg).

Sodium borohydride (3mg) was added to an ethanol (3ml) solution of the obtained diamide compound (10:R=2,2-dimethylcyclopropane) (14mg) and stirred at the room temperature for 2 hours. After the completion of the reaction, the solvent was distilled out, and then purified by using silica gel thin-layer chromatography (ethyl acetate, hexane), thus obtained an alcohol compound (11:R=2,2-dimethylcyclopropane) (5mg) of the objective compound of example 4.

1H-NMR (300MHz, $CDCl_3$) δ =0.80-0.92 (2H, m), 1.15-1.24 (14H, m), 1.37-1.47 (2H, m), 5.80 (1H, s), 7.28 (2H, d,J=8.7Hz), 7.35-7.43 (1H, brs), 7.49 (2H, d, J=8.7Hz), 7.60-7.67 (1H, m), 8.14 (1H, d, J=8.7Hz), 8.19-8.23 (1H, m), 8.30-8.40 (1H, brs). MS(ESI) m/z 408$(M+H)^+$.

(Example 5)

20%-palladium hydroxide on carbon (1mg) and 4M hydrochloric acid (50mg) were added to an ethanol solution (2ml) of the alcohol compound obtained in example 4 (11:R=2,2-dimethylcyclopropane) (3mg), and then the solution was subjected to the hydrogen substitution and stirred at 50℃ for 4 hours. After the reaction having been completed, the solid matter was filtered out, and the filtrate was extracted with ethyl acetate and further washed, dried and concentrated according to the conventional manner, followed by the purification with the silica gel chromatography (ethyl acetate, hexane), thus obtained a methylene compound

of the objective compound of example 5 (12:R=2,2-dimethylcyclopropane) (1mg). 1H-NMR (300MHz, $CDCl_3$), δ =0.80-0.90 (2H, m), 1.21-1.28 (14H, m), 1.34-1.42 (2H, m), 3.88 (2H, s), 7.06-7.13 (4H, m), 7.40-7.49 (4H, m), 8.06-8.12 (1H, m). MS(ESI) m/z 392$(M+H)^+$.

(Example 6)

Process 1: Synthesis of 5-acetamide-2-trimethylstannylpyridine

An acetic acid solution (80ml) of 2-bromo-5-nitropyridine (3g, 14.8mmol) and iron (25g, 446mmol) was stirred at the room temperature for 15 hours. After the reaction was completed and the solvent was distilled out, the resultant was extracted by using ethyl acetate, and then further washed, dried and concentrated according to the conventional manner, thus obtained 5-amino-2-bromopyridine (2.26g, 89%) as a white crystal.

To an acetic anhydride solution (1.5ml) of the obtained 5-amino-2-bromopyridine (1.75g, 10.2mmol), pyridine (3ml) was added and stirred at the room temperature for 6 hours. After the reaction having been completed, the solvent was distilled out, and the resultant was extracted with ethyl acetate and washed, dried and concentrated according to the conventional manner, thus obtained 5-acetamide-2-bromopyridine (2.135g, 98%) in the form of a white crystal.

A toluene (100ml) solution of the obtained 5-acetamide-2-bromopyridine (1.3g, 6mmol), hexamethylditin (5g, 15.3mmol) and tetrakis (triphenylphosphine) palladium (1g, 0.87mmol) was stirred at 100℃ under the argon atmosphere for 6 hours. After the reaction having been completed, the solid matter was filtered out and the filtrate was extracted with ethyl acetate, and washed, dried and concentrated according to the conventional manner, followed by the purification by using silica gel chromatography (ethyl acetate, hexane), thus obtained 5-acetamide-2-trimethylstannylpyridine (1.45g, 80%).

1H-NMR (300MHz, $CDCl_3$), δ =0.33 (9H, s), 2.19 (3H, s), 7.68 (1H, d, J=7.8Hz), 8.04 (1H, dd, J=7.8, 2.4Hz), 8.66 (1H, d, J=2.4Hz). MS(ESI) m/z 301$(M+H)^+$.

Then, according to the same method as that in the process 3 of example 4, a compound of example 6 was synthesized by using the above 5-acetamide-2-trimethylstannylpyridine and the palladium complex obtained in the process 2 compound of example 4 (7) as a starting material.

1H-NMR (300MHz, $CDCl_3$), δ =0.78-0.91 (2H, m), 1.16-1.26 (14H, m), 1.36-1.46 (2H, m), 5.68 (1H, s), 7.03-7.10 (1H, m), 7.22-7.31 (2H, m), 7.38-7.52 (2H, m), 7.94-8.02 (1H, m), 8.51-8.57 (1H, m). MS(ESI) m/z 408$(M+H)^+$.

(Example 7)

According to the same method as of example 5, a compound of example 7 was synthesized by using example 6 compound as a starting material.

1H-NMR (300MHz, $CDCl_3$) δ =0.78-0.92 (2H, m), 1.16-1.28 (14H, m), 1.35-1.46 (2H, m), 4.06 (2H, s), 7.05 (1H, d, J=8.7Hz), 7.16 (2H, d, J=7.8Hz), 7.27-7.36 (1H, m), 7.37-7.50 (3H, m), 8.02-8.09 (1H, m), 8.44 (1H, d, J=2.7Hz). MS(ESI m/z 392$(M+H)^+$.

(Example 8)

Process 1: Synthesis of 3-amino-6-(4-nitrophenoxy) pyridazine

3-amino-6-chloropyridazine (520mg, 4mmol) and 4-nitrophenol (1.39g, 10mmol) were suspended in a 1M sodium hydroxide aqueous solution (10ml) and heated in a sealed tube at 160℃ for 18 hours. After the reaction was completed, dichloromethane (30ml) was added to thereto for extraction, and after the organic layer was washed with 1M sodium hydroxide aqueous solution (10ml), the resultant was dried with sodium sulfide. After the solvent was distilled out, the resultant was purified by using a silica gel TLC plate (dichloromethane, methanol), thus obtained 3-amino-6-(4-nitro-phenoxy) pyridazine (69mg, 7%).

1H-NMR (300MHz, DMSO d6), δ =6.42 (2H, s), 6.99 (1H, d, J=9.3Hz), 7.25 (1H, d

J=9.6Hz), 7.27 (2H, d, J=9.3Hz), 8.26 (2H, d, J=9.0Hz). MS(ESI) m/z 233$(M+H)^+$.

Process 2: Production of 3-amino-6-(4-aminophenoxy) pyridazine

$FeSO_4 \cdot 7H_2O$ (834mg, 3mmol) was added into a mixed solvent of ethanol (1ml) and water (5ml) of the pyridazine obtained in the process 1, and stirred at 100℃ for 10 minutes, and after the solution having been cooled to the room temperature, ammonia water (0.25ml) was added thereto. The resulting black tarry substance was subjected to decantation with ethyl acetate (5 times, each by 5ml), and after the ethyl acetate solution having been collected, it was washed with water and dried with sodium sulfide. After the solvent having been distilled out, the resultant was purified by using a silica gel TLC plate (dichloromethane, methanol), thus obtained 3-amino-6-(4-aminophenoxy) pyridazine (23mg, 57%).

1H-NMR (300MHz, DMSO-d6) δ =4.92 (2H, s), 6.05 (2H, s), 6.55 (2H, d, J=8.7Hz), 6.75 (2H, d, J=8.7Hz), 6.87 (1H, d, J=9.3Hz), 6.96 (1H, d, J=9.3Hz). MS(ESI) m/z 203$(M+H)^+$, 405$(2M+H)^+$.

Process 3: Synthesis of example 8 compound

An acetonitrile (2ml) solution of the diamine compound (23mg, 0.11mmol) obtained in the process 2 was added with pyridine (0.05ml, 0.5mmol) under the ice-water cooling and further added with 2,2-dimethylcyclopropanecarbonyl chloride (45mg, 0.33mmol), and then stirred at the room temperature for 15 minutes. After water (0.03ml) was added thereto, the solvent was distilled out therefrom and purified by using a silica gel TLC plate (dichloromethane, methanol), thus obtained compound of example 8 (30mg, 70%).

1H-NMR (300MHz, DMSO-d6) δ =0.79-0.89 (2H, m), 0.97-1.05 (2H, m), 1.17-1.21 (12H), 1.66 (2H, dd, J=8.1, 5.1Hz), 1.91 (1H, dd, J=7.8, 5.7Hz), 7.11 (2H, dd, J=6.9, 2.4Hz), 7.40 (1H, d, J=9.6Hz), 7.64 (2H, d, J=9.0Hz), 8.35 (1H, d, J=9.6Hz), 10.12 (1H, s), 11.13 (1H, s). MS(ESI) m/z 395$(M+H)^+$.

(Example 9)

Process 1:

A dimethylformamide (25ml) suspension of 2-amino-5-nitropyridine (703mg, 5mmol), 1-iodo-4-nitrobenzene (1.25g, 5mmol), copper (34mg, 0.5mmol) and potassium carbonate (1.38g, 10mmol) was stirred at 100℃ for 13 hours. After the reaction having been completed, the extraction was applied to the solution by adding dichloromethane (200ml) and water (100ml), and after the organic layer having been washed with water (100ml) by three times, it was dried with magnesium sulfate and concentrated. The concentrate was dissolved into tetrahydrofuran (50ml) and concentrated, and then added with dichloromethane (20ml) and n-hexane (20ml) so to be crystallized, thus obtained a dinitro compound (0.90g, 69%).

1H-NMR (300MHz, DMSO-d6) δ =8.07 (2H, d, J=9.3Hz), 8.28 (2H, d, J=9.3Hz), 9.35(2H, s), 11.41(1H, s).

Process 2:

The dinitro compound obtained in the process 1, (506mg, 2mmol) was dissolved into acetonitrile (50ml) and tetrahydrofuran (25ml), which in turn was mixed with 10%-palladium carbon (283mg) to cause the hydrogen substitution, and reduced under normal pressure. After the reaction having been completed, the sellaite filtering was used to remove the palladium carbon and the solvent was distilled out, thus obtained the diamine compound (0.38g, 98%).

1H-NMR (300MHz, DMSO-d6) δ =4.56 (2H, brs), 4.57 (2H, brs), 6.47 (2H, d, J=8.4Hz), 7.26 (2H, d, J=8.7Hz), 7.86 (2H, s), 8.35 (1H, s).

Process 3:

An acetonitrile (10ml) solution of the diamine compound (102mg, 0.5mmol) was added with pyridine (0.10ml, 1mmol) under the ice-water cooling and further added with 2,2-dimethylcyclopropanecarbonyl chloride (143mg, 1mmol), and then stirred at the room temperature for 20 hours. After water (1ml) having been

added thereto, the solvent was distilled out therefrom and a silica gel TLC plate (dichloromethane, methanol) was used for purification, and thus example 9 compound (150mg, 75%) was obtained.

1H-NMR (300MHz, DMSO-d6) δ =0.75 (1H, dd, J=8.1Hz, J=3.9Hz), 0.81 (1H, dd, J=7.7Hz, J=3.8Hz), 0.93-1.01 (2H, m), 1.14-1.19 (12H, s), 1.63 (2H, dd, J=8.0Hz, J=5.3Hz), 7.74 (2H, d, J=9.0Hz), 7.60 (2H, d, J=9.0Hz), 8.61 (2H, s), 9.40 (1H, s), 9.91 (1H, s), 10.07 (1H, s). MS(ESI) m/z 394$(M+H)^+$.

(Example 10)

Process 1: Synthesis of 1-hydroxy-3-(4-nitrophenyl)-2-propanone

4-nitrophenylacetic acid (1.00g, 6mmol) was added into a dichloromethane solution of oxalyl chloride (11mmol, 11ml) and stirred at a temperature range of room temperature to 40℃ for 4.5 hours. A crystal of acid chloride, which had been obtained by distilling out the solvent, was added with tris (trimethylsilyloxy) ethylene (4.6ml, 14mmol) and further added with 6 drops of $SnCl_4$ under water cooling, and then stirred at the room temperature for 15 hours. The resultant was added with 1,4-dioxane (10ml) and 1M hydrochloric acid (5ml), and stirred at the room temperature for 30 minutes and at 90℃ for another 30 minutes. After cooling, dichloromethane (10ml) and water (10ml) were added into it to wash, and further the organic layer was washed with a saturated sodium hydrogencarbonate. Also, each of the aqueous layers was re-extracted with dichloromethane (20ml) by one time for each so as to be mixed with the organic layer. The recovered organic layer was dried with magnesium sulfate, and the solvent was distilled out, thus obtained 1-hydroxy-3-(4-nitrophenyl)-2-propanone (579mg, 54%).

1H-NMR (300MHz, $CDCl_3$) δ =2.93 (1H, t, J=3.9Hz), 3.86 (2H, s), 4.37 (2H, d, J=3.9Hz), 7.41 (2H, d, J=8.7Hz), 8.22 (2H, d, J=8.7Hz).

Process 2: Synthesis of 1-chloro-3-(4-nitrophenyl)-2-propanone (19)

An acetonitrile (4ml) solution of the compound obtained in the process 1

(120mg, 0.6mmol) was added with pyridine (0.055ml, 0.7mmol), thionyl chloride (0.045ml, 0.7mmol) and 1 drop of dimethylformaldehyde under water cooling, and after having been stirred at 40℃ for 3 hours, it was further added with pyridine (0.025ml, 0.3mmol) and thionyl chloride (0.020ml, 0.3mmol) and stirred. After the reaction having been completed, the solvent was distilled out, and the resultant was purified with a silica gel TLC plate (n-hexane, ethyl acetate), thus obtained 1-chloro-3-(4-nitrophenyl)-2-propanone (19:115mg, 88%).

1H-NMR (300MHz, $CDCl_3$) δ =4.07 (2H, s), 4.15 (2H, s), 7.40 (2H, d, J=8.7Hz), 8.22 (2H, d, J=8.7Hz). MS(ESI) m/z 212$(M-H)^-$.

Process 3: Synthesis of 2-amino-5-(4-nitrobenzyl) thiazole (20)

Thiocarbamide (54mg, 0.7mmol) was added to an ethanol (9ml) suspension of the chloro compound (19) (150mg, 0.7mmol) obtained in the process 2 and stirred at 60℃ for 7 hours. After the solvent having been distilled out, the obtained crystal was washed with acetonitrile, thus obtained 2-amino-5-(4-nitrophenylbenzyl) thiazole (20) (135mg, 82%).

1H-NMR (300MHz, DMSO-d6) δ =4.04 (2H, s), 6.56 (1H, s), 7.56 (2H, d, J=9.0Hz), 8.21 (2H, d, J=8.4Hz). MS(ESI) m/z 236$(M+H)^+$.

Process 4: Synthesis of 2-amino-5-(4-aminobenzyl)thiazole (21)

The thiazole (20) (123mg, 0.5mmol) obtained in the process 3 was added to an acetic acid (10ml) suspension of zinc (1.03g, 16mmol), which had been washed and activated by 1M hydrochloric acid, and stirred at the room temperature for 30minutes. After the zinc having been filtered out, the filtrate was poured into an aqueous solution of dichloromethane (100ml) and 2M sodium hydroxide aqueous solution (78ml) under the ice water cooling. This organic layer and another organic layer, which was obtained by applying another extraction with the dichloromethane (totally 105ml) to the aqueous layer, were mixed, and then the mixture was dried with sodium sulfate, and the solvent was distilled out, thus

obtained 2-amino-5-(4-aminobenzyl)thiazole (21) (89mg, 83%).

1H-NMR (300MHz, DMSO-d6) δ =3.52 (2H, s), 4.82 (2H, s), 5.99 (1H, s), 6.47 (2H, d, J=8.4Hz), 6.75 (2H, s), 6.86 (2H, d, J=8.1Hz). MS(ESI) m/z 206$(M+H)^+$.

Process 5: Synthesis of a compound of example 10

A dichloromethane (12ml) suspension of the thiazole (21) (60mg, 0.3mmol) obtained in the process 4 was added with pyridine (0.060ml, 0.7mmol) under water cooling and further added with 2,2-dimethylcyclopropanecarbonyl chloride (146mg, 1.1mmol), and then stirred at the room temperature. After 3 hours, water (10ml) was added into the solution for washing. The organic layer was dried with magnesium sulfate, and then the oil obtained by distilling out the solvent was purified by using a silica gel TLC plate (n-hexane, ethyl acetate), thus obtained example 10 compound (60mg, 50%).

1H-NMR (300MHz, $CDCl_3$) δ =0.74 (1H, dd, J=7.8, 3.6Hz), 0.86 (1H, dd, J=7.8, 3.9Hz), 0.94 (1H, dd, J=5.4, 3.6Hz), 0.99 (1H, dd, J=5.1, 3.6Hz). 1.09 (3H, s), 1.11 (3H, s), 1.12 (3H, s), 1.13 (3H, s), 1.61 (1H, dd, J=7.8, 5.4Hz), 1.74 (1H, dd, J=7.8, 5.4Hz), 6.70 (1H, s), 7.11 (2H, d, J=8.4Hz), 7.47 (2H, d, J=8.4Hz), 9.96 (1H, s), 12.15 (1H, s). MS(ESI) m/z 398$(M+H)^+$.

(Example 11)

According to the same method as that used in the process 2 of example 1, a compound of example 11 was synthesized by using 5-amino-2-(4-aminophenyl) pyridine as a starting material.

1H-NMR (300MHz, $CDCl_3$) δ =0.80-0.91 (2H, m), 1.16-1.30 (14H, m), 1.38-1.48 (2H, m), 7.30-7.72 (5H, m), 7.90 (2H, d, J=8.4Hz), 8.22-8.30 (1H, m), 8.52-8.55 (1H, m). MS(ESI) m/z 378$(M+H)^+$.

(Example 12)

A dimethylformamide (10ml) solution of 2-hydroxy-5-nitropyridine (13) (700mg, 5mmol) was added with sodium hydride (240mg, 12mmol) and fo th

added with 4-nitrobenzylbromide (14:X=Br) (1.08g, 5mmol), and then stirred at the room temperature for 20 hours. After the reaction having been completed, the solution was extracted with ethyl acetate, washed, dried and concentrated according to the conventional manner, followed by the purification by using silica gel chromatography (dichloromethane, ethyl acetate), thus obtained the dinitro compound (15). This dinitro compound (15) was dissolved into an ethanol (50ml), which was in turn added with 5%-palladium carbon (100mg) to perform the hydrogen substitution and then reduced under the normal pressure. After the reaction having been completed, the palladium carbon was removed by the celite filtering, and after the solvent was distilled out, the resultant was purified by way of silica gel column chromatography (ethyl acetate), thus obtained the diamine compound (16) (430mg, 40%).

Then, according to the same method as that used in the process 2 of example 1, example 12 compound was synthesized by using the diamine compound (16) as a starting material.

1H-NMR (300MHz, DMSO-d6) δ =0.73-.80 (2H, m), 0.90-1.00 (2H, m), 1.10-1.19 (12H, m), 1.50-1.58 (1H, m), 1.60-1.68 (1H, m), 4.97 (1H, d, J=12.4Hz), 5.30 (1H, d, J-12.4Hz), 6.43 (1H, d, J=9.9Hz), 7.20 (2H, d, J=8.4Hz), 7.41 (1H, dd, J=9.9, 3.0Hz), 7.54 (2H, d, J=8.4Hz), 8.12 (1H, d, J=3.0Hz), 9.82 (1H, brs), 10.08 (1H, brs).

MS(ESI) m/z 408$(M+H)^+$.

(Example 13)

According to the same method as example 12, a compound of example 13 was synthesized by using 2-hydroxy-5-nitropyridine and 2-(4-nitrophenyl)ethyl bromide as a starting material.

1H-NMR (300MHz, DMSO-d6) δ =7.30-0.80 (2H, m), 0.90-0.99 (2H, m), 1.10-1.18 (12H, m), 1.50-1.58 (1H, m), 1.60-1.67 (1H, m), 2.84 (2H, t, J=7.5Hz), 4.02 (2H, t, J=7.5Hz), 6.38 (1H, d, J=9.6Hz), 7.11 (2H, d, J=8.7Hz), 7.37 (1H, dd, J=9.6,

3.0Hz), 7.50 (2H, d, J=8.7Hz), 8.01 (1H, d, J=3.0Hz), 9.75 (1H, s), 10.00 (1H, s). MS(ESI) m/z 422$(M+H)^+$.

(Example 14)

Process 1:

A dimethylformamide (20ml) solution of 2-mercapto -5-nitro-pyridine (1.56g, 10mmol) was added with 60% sodium hydride (446mg, 11mmol) and further added with 1-bromomethyl-4-nitrobenzene (2.14g, 10mmol), and then stirred at the room temperature for 1.5 hours. The reacted mixture was added into water (100ml) to precipitate solid matter and the solid matter was filtered. The solid matter was added with dichloromethane (100ml) to be dissolved therein, and washed with water (60ml). This organic layer and another organic layer, which was obtained by applying 2 times of extraction with the dichloromethane (20ml) to the aqueous layer, were mixed, and after having been dried with magnesium sulfate, distilled out the solvent, thus obtained a dinitro compound (2.51g, 87%).

1H-NMR (300MHz, DMSO-d6) δ =4.68 (2H, s), 7.62 (1H, dd, J=8.9Hz, J=0.8Hz), 7.74 (2H, d, J-8.7Hz), 8.17 (2H, d, J=8.7Hz), 8.39 (1H, dd, J=9.0Hz, J=2.7Hz), 9.25 (1H, dd, J=2.9Hz, J=0.8Hz).

Process 2:

A tetrahydrofuran (1.5ml) solution of the dinitro compound (218mg, 0.7mmol) was added to an acetic acid (10ml) suspension of zinc (1.36g, 21mmol), which had been washed and activated with 1M hydrochloride, and then stirred at the room temperature for 16 hours. After the zinc having been filtered out, the filtrate was poured into an aqueous solution of ethyl acetate (100ml) and 2M sodium hydrate (110ml) under the ice water cooling. The organic layer was washed with water (50ml) and thereafter dried with magnesium sulfate so as to distill out the solvent. The concentrate was added with dichloromethane (50ml) so as to be dissolved therein and then washed with an aqueous solution of 1M

sodium hydroxide (30ml) and water (30ml), and after the organic layer was dried with the magnesium sulfate to distill out the solvent, the resultant was purified by using silica gel TLC plate (hexane, ethyl acetate), thus obtained a mixture including a diamine comopund. A dichloromethane (10ml) solution of this mixture (66mg) was added with triethylamine (0.085ml, 0.6mmol) under the ice water cooling and further added with 2,2-dimethylcyclopropanecarbonyl chloride (85mg, 0.6mmol), and then stirred at the room temperature for 17 hours. After water (10ml) having been added into the resultant solution, the organic layer was dried with the magnesium sulfate to distill out the solvent, the resultant was purified with a silica gel TLC plate (dichloromethane, methanol), thus obtained example 14 compound (18mg) of the target.

1H-NMR (300MHz, DMSO-d6) δ =0.73-0.84 (2H, m), 0.93-1.02 (2H, m), 1.12-1.18 (12H, s), 1.59-1.68(2H, m), 4.3 (2H, s), 7.23 (1H, d, J=8.7Hz), 7.27 (2H, d, J=9.0Hz), 7.49 (2H, d, J=8.1Hz), 7.89 (1H, dd, J=8.7Hz, J=2.7Hz), 8.66 (1H, d, J=2.7Hz), 10.03 (1H, s), 10.23 (1H, s). MS(ESI) m/z 424$(M+H)^+$.

(Example 15)

Process 1:

4-amino-1-benzylpiperidine (100mg, 0.526mmol) was dissolved into dichloromethane (10ml) and then added with triethylamine (150mg, 1.5mmol) and 2,2-dimethylcyclopropanecarbonyl chloride (159mg, 1.2 mmol), which was further stirred at the room temperature for 14 hours. After the reaction was completed, the resultant was extracted with ethyl acetate and then washed, dried and concentrated according to the conventional manner and purified by using silica gel column chromatography (ethyl acetate, hexane), thus obtained a white crystal of 4-(2,2-dimethylcyclopropanecarbonylamino)-1-benzylpiperidine. The white crystal was dissolved into an ethanol (10ml)-ethyl acetate (1ml) mixed solvent, wherein 5% palladium carbon (150mg) and formic acid (160mg) were dissolved

into the ethanol (10ml) and applied thereto with dropping, which was stirred at the room temperature over night. After the palladium was filtered, the solvent was distilled out and aqueous solution of 2M sodium hydroxide was added therein to make pH>13, the solution was extracted with dichloromethane and further washed with a saturated saline solution, dried and vacuum concentrated, thus obtained 4-(2,2-dimethylcyclopropanecarbonylamino) piperidine (23 : R = 2,2-dimethylcyclopropane) (11.2mg, 11%).

1H-NMR (300MHz, $CDCl_3$) δ =0.68-0.72 (1H, m), 1.06-1.09 (1H, m), 1.13-1.38 (7H, m), 1.78 (2H, s), 1.88-1.97 (2H, m), 2.69 (2H, t, J=12.6Hz), 3.06 (2H, td, J=3.3, 12.6Hz), 3.88-3.95 (1H, m), 5.49 (1H, s). MS(ESI) m/z 197$(M+H)^+$.

Process 2:

4-nitrobenzyl bromide (24:X=Br) (110mg, 0.5mmol), potassium carbonate (352mg, 2.55mmol) and sodium iodide (76.5mg, 0.5mmol) were added to a dimethylformamide (5ml) solution of the piperidine (23) obtained in the process 1, and then stirred under the argon atmosphere at the room temperature for 2 hours. This was further stirred at 70℃ for 1 hour and was extracted with hexan-ethyl acetate (3:1) mixed solvent, and then washed with water and saturated saline solution, dried and vacuum concentrated, thus obtained a 4-nitrobenzylpiperadine compound (25:R= 2,2-dimethylcyclopropane) in the form of a yellow crystal (95mg, 57%).

1H-NMR (300MHz, $CDCl_3$) δ =0.69-0.73 (1H, m), 1.07 (1H, t, J=4.8Hz), 1.13 (3H, s), 1.15 (3H, s), 1.19-1.24 (1H, m), 1.41-1.49 (1H, m), 1.93 (2H, brs), 2.12-2.21 (2H, m), 2.78 (2H, d, J=11.7Hz), 3.58 (2H, s), 3.75-3.88 (1H, m), 5.42-5.46 (2H, m), 7.50 (2H, d, J=8.4Hz), 8.17 (2H, d, J=8.4Hz). MS(ESI) m/z 332 $(M+H)^+$.

Process 3:

An acetic acid (3ml) solution of the 4-nitrobenzylpiperidine compound (25) (65.8mg, 0.2mmol) obtained in the process 2 was added with zinc (300mg) little by

little at 0℃. After having been stirred at the room temperature for 2 hours, this was filtered to be taken out, had the solvent distilled out and neutralized with 2M aqueous sodium hydroxide, and then was extracted with ethylacetate. The resultant was washed with water and the saturated saline solution, dried and then vacuum concentrated, thus obtained a 4-aminobenzylpiperidine compound (26:R= 2,2-dimethylcyclopropane) in the form of a yellow oily matter (50mg, 85%).

1H-NMR (300MHz, $CDCl_3$) δ =0.67-0.73 (1H, m), 1.07-1.25 (8H, m), 1.44-1.55 (2H, m), 1.89 (2H, brs), 2.05-2.15 (2H, m), 2.82-2.86 (2H, m), 3.44 (2H, s), 3.70 (1H, brs), 4.48 (1H, s), 6.64 (2H, d, J=8.4Hz), 7.08 (2H, d, J=8.4Hz). MS(ESI) m/z 302 $(M+H)^+$.

Process 4:

The 4-aminobenzylpiperidine compound (26) (50mg, 0.17mmol) obtained in the process 3 was used to cause the same reaction as process 2 of example 1, thus obtained example 15 compound (27:R= 2,2-dimethylcyclopropane) in the form of a yellow-white crystal (14.9mg, 22%).

1H-NMR (300MHz, $CDCl_3$) δ =0.68-0.72 (1H, m), 0.81-0.85 (1H, m), 1.04-1.09 (1H, m), 1.09-1.23 (14H, m), 1.40-1.45 (1H, m), 1.49-1.58 (1H, m), 1.87-1.92 (2H, m), 2.10-2.19 (2H, m), 2.84 (2H, m), 3.51 (2H, s), 3.74-3.85 (1H, m), 5.50 (2H, d, J=8.4Hz), 7.26 (2H, d, J=8.4Hz), 7.48 (2H, d, J=8.4Hz), 7.55 (1H, s). MS(ESI) m/z 398$(M+H)^+$.

(Example 16)

Process 1:

An acetonitrile (5ml) solution of the piperidine compound (23:R= 2,2-dimethylcyclopropane) (50mg, 0.25mmol) obtained in the process 1 of example 15 was added with 2-(4-t-butoxycarbonylaminophenyl)ethanol paratoluensulfonate (57mg, 0.31mmol), sodium carbonate (32mg, 0.31mmol) and sodium iodide (2mg), which was in turn heated and refluxed at 100℃ for 2 hours. The resultant was

extracted with ethyl acetate, and further washed with water and saturated saline solution, dried and vacuum concentrated, and then separately purified with a silica gel TLC plate (chloroform, methanol), thus obtained a phenethylpiperidine compound (31mg, 29%).

1H-NMR (300MHz, $CDCl_3$) δ =0.69-0.74 (1H, m), 1.08 (1H, t, J=4.8Hz), 1.13 (3H, s), 1.66 (3H, s), 1.20-1.26 (2H, m), 1.50-1.64 (2H, m), 1.51 (9H, s), 1.95 (2H, brs), 2.17-2.20 (2H, m), 2.57-2.62 (2H, m), 2.74-2.79 (2H, m), 2.94-2.99 (2H, m), 3.77-3.88 (1H, m), 5.45-5.48 (1H, m), 6.45 (1H, s), 7.10 (2H, d, J=8.4Hz), 7.23-7.28 (2H, m).

Process 2:

4M hydrochloric acid-dioxane solution was dropped by 1ml into a dichloromethane (3ml) solution of the phenethylpiperidine (30.9mg, 0.074mmol) obtained in the process 1, which was in turn stirred at the room temperature for 3 hours. Further, 4M hydrochloric acid-dioxane solution was added by another 1ml to the solution, which was then stirred again at the room temperature for 1 hour. After the solvent was distilled out, the resultant was extracted with ethyl acetate, and washed with saturated aqueous solution of sodium hydrogen carbonate, water and saturated saline solution, dried and then vacuum concentrated, thus obtained a deprotected compound in the form of a light yellow crystal (9.7mg, 41%).

1H-NMR (300MHz, $CDCl_3$) δ =0.69-0.74 (1H, m), 1.08 (1H, t, J=4.8Hz), 1.14 (3H, s), 1.67 (3H, s), 1.20-1.26 (2H, m), 1.50-1.64 (2H, m), 1.95 (2H, brs), 2.19-2.25 (2H, m), 2.57-2.62 (2H, m), 2.70-2.76 (2H, m), 2.98-3.02 (2H, m), 3.58 (2H, brs), 3.58-3.78 (1H, m), 5.45-5.48 (1H, m), 6.62 (2H, d, J=8.4Hz), 6.98 (2H, d, J=8.4Hz). MS(ESI) m/z 316 $(M+H)^+$.

Process 3:

The deprotected compound obtained in the process 2 was used as a starting material, which experienced the same reaction as the process 2 of example 1, and a

compound of example 16 was obtained in the form of a yellow-white crystal (3.8mg, 31%).

1H-NMR (300MHz, $CDCl_3$) δ =0.69-0.74 (1H, m), 0.81-0.86 (1H, m), 1.08 (1H, t, J=4.8Hz), 1.13-1.26 (14H, m), 1.37-1.41 (1H, m), 1.54-1.64 (2H, m), 1.94-2.00 (2H, m), 2.20-2.29 (2H, m), 2.61-2.67 (2H, m), 2.78-2.84 (2H, m), 3.01-3.05 (2H, m), 3.81-3.88 (1H, m), 5.47 (1H, d, J=8.7Hz), 7.13 (2H, d, J=8.4Hz), 7.14 (1H, s), 7.43 (2H, d, J=8.4Hz). MS(ESI) m/z 412$(M+H)^+$.

(Example 17)

According to the same method as of example 1, a compound of example 17 was synthesized by using 3-nitrophenol and 2-chloro-5-nitropyridine as a starting material.

1H-NMR (300MHz, DMSO-d6) δ =0.74-0.84 (2H, m), 0.94-1.02 (2H, m), 1.12 (3H, s), 1.15 (6H, s), 1.17 (3H, s), 1.60-1.67 (2H, m), 6.70-6.76 (1H, m), 6.99 (1H, d, J=8.7Hz), 7.24-7.44 (3H, m), 8.08 (1H, dd, J=8.7, 2.7Hz), 8.35 (1H, d, J=2.7Hz), 10.14 (1H, brs), 10.25 (1H, brs). MS(ESI) m/z 394$(M+H)^+$.

(Example 18)

According to the same method as of example 1, a compound of example 18 was synthesized by using 2-nitrophenol and 2-chloro-5-nitropyridine as a starting material.

1H-NMR (300MHz, DMSO-d6) δ =0.82-0.87 (2H, m), 0.98-1.03 (2H, m), 1.12-1.18 (14H, m), 1.64-1.70 (2H, m), 6.96-7.17 (3H, m), 7.43 (1H, d, J=8.4Hz), 8.08 (1H, dd, J=8.4, 3.0Hz), 8.27-8.31 (1H, m), 8.59 (1H, d, J=3.0Hz), 9.42 (1H, s), 10.22 (1H, s). MS(ESI) m/z 394$(M+H)^+$.

(Example 19)

According to the same method as of example 12, a compound of example 19 was synthesized by using 2-hydroxy-5-nitropyridine and 3-nitrobenzylbromide as a starting material.

1H-NMR (300MHz, DMSO-d6) δ =0.74-0.80 (2H, m), 0.90-1.02 (2H, m), 1.10-1.28 (12H, s), 1.52-1.57 (1H, m), 1.61-1.68 (1H, m), 4.96-5.13 (2H, m), 6.46 (1H, d, J=9.3Hz), 6.90 (1H, d, J=8.1Hz), 7.24 (1H, t, J=8.1Hz), 7.40 (1H, s), 7.44 (1H, dd, J=9.3, 3.0Hz), 7.60 (1H, d, J=8.1Hz), 8.13 (1H, d, J=3.0Hz), 9.83 (1H, s), 10.08 (1H, s). MS(ESI) m/z 408$(M+H)^+$.

(Example 20)

According to the same method as of example 12, a compound of example 20 was synthesized by using 2-hydroxy-5-nitropyridine and 2-nitrobenzylbromide as a starting material.

1H-NMR (300MHz, DMSO-d6) δ =0.76-0.85 (2H, m), 0.92-1.00 (2H, m), 1.10-1.20 (12H, s), 1.68-1.72 (2H, m), 5.02-5.20 (1H, m), 6.55 (1H, d, J=9.6Hz), 7.08 (1H, d, J=7.5Hz), 7.22-7.32 (1H, m), 7.50 (1H, dd, J=9.6, 3.0Hz), 7.77-7.86 (1H, m), 8.08 (1H, d, J=7.5Hz), 8.29 (1H, d, J=3.0Hz), 10.02 (1H, s), 10.39 (1H, s). MS(ESI) m/z 408$(M+H)^+$.

(Example 21)

According to example 8, a compound of example 21 was synthesized by using 3-amino-6-chloropyridazine and 3-nitrophenol as a starting material.

1H-NMR (300MHz, DMSO-d6) δ =0.78 (1H, dd, J-7.8Hz, 3.9Hz), 0.85 (1H, dd, J=7.5Hz, 3.9Hz), 0.96 (1H, dd, J=6.0Hz, 4.5Hz), 1.02 (1H, dd, J=5.4Hz, 4.2Hz), 1.11-1.20 (12H, s), 1.64(1H, dd, J-7.8Hz, 5.4Hz), 1.92 (1H, dd, J=7.8Hz, 5.7Hz), 6.81 (1H, ddd, J=7.8Hz, 2.3Hz, 1.5Hz), 7.32 (1H, t, J=8.0Hz), 7.31 (1H, m), 7.44 (1H, d, J=9.6Hz), 7.51 (1H, m), 8.37 (1H, d, J=9.3Hz), 10.20 (1H, s), 11.16 (1H, s). MS(ESI) m/z 395$(M+H)^+$.

(Example 22)

According to the same method as of example 1, a compound of example 22 was synthesized by using 2-chloro-5-nitropyridine and 3-methyl-4-nitrophenol as a starting material.

1H-NMR (300MHz, DMSO-d6) δ =0.75-0.81 (2H, m), 0.97 (2H, q, J=6.0, 10.2Hz), 1.16 (12H), 1.65 (1H, t, J=8.1Hz), 1.73 (1H, t, J=8.1Hz), 2.17 (3H, s), 6.85 (1H, d, J=9.0Hz), 6.92-6.97 (2H), 7.30 (1H, d, 8.4Hz), 8.06 (1H, dd, J=2.7, 9.0Hz), 8.3 (1H, d, J=2.7Hz), 9.41 (1H, s), 10.2 (1H, s). MS(ESI) m/z 408$(M+H)^+$, 406$(M-H)^-$.

(Example 23)

According to the same method as of example 1, a compound of example 23 was synthesized by using 2-chloro-4-methyl-5-nitropyridine and 4-nitrophenol as a starting material.

1H-NMR (300MHz, DMSO-d6) δ =0.75-0.81 (2H, m), 0.98-1.00 (2H, m), 1.14 (6H, s), 1.17 (6H, s), 1.59-1.73 (2H, m), 2.19 (3H, s), 6.85 (1H, s), 7.01 (2H, d, J=9.0Hz), 7.60 (2H, d, J=9.0Hz), 7.96 (1H, s). MS(ESI) m/z 408$(M+H)^+$, 406$(M-H)^-$.

(Example 24)

According to the same method as of example 1, a compound of example 24 was synthesized by using 2-chloro-4-methyl-5-nitropyridine and 3-methyl-4-nitrophenol as a starting material.

1H-NMR (300MHz, $CDCl_3$) δ =0.82-0.90 (2H, m), 1.15-1.30 (14H), 1.42-1.56 (2H, m), 2.28 (6H, s), 6.73 (1H, brs), 6.94 (2H, brs), 7.09 (2H, brs), 7.74 (1H, brs), 8.19 (1H, brs). MS(ESI) m/z 422$(M+H)^+$, 420$(M-H)^-$.

(Example 25)

According to the same method as that used in the process 2 of example 1, a compound of example 25 was synthesized by using 6-(5-amino-2-pyridylthio)-3-pyridylamine as a starting material.

1H-NMR (300MHz, DMSO-d6) δ =0.78-0.85 (2H, m), 0.97-1.05 (2H, m), 1.14 (6H, m), 1.16 (6H, s), 1.64-1.69 (2H, m), 7.2 (2H, d, J=8.7Hz), 8.00 (2H, dd, J=8.7, 2.7Hz), 8.67 (2H, d, J=2.7Hz), 10.37 (2H, s). MS(ESI) m/z 411$(M+H)^+$.

(Example 26)

According to the same method as that used in the process 2 of example 1, a

compound of example 26 was synthesized by using 2,2-dichloro-cyclopropanecarbonylchloride as a starting material.

1H-NMR (300MHz, DMSO-d6) δ =2.02 (2H, d, J=9.0Hz), 2.50 (2H, s), 2.87 (2H, t, J=9.0Hz), 7.01 (1H, d, J=8.7Hz), 7.09 (2H, d, J=8.7Hz), 7.62 (2H, d, J=8.7Hz), 8.09 (1H, dd, J=3.0, 8.7Hz), 8.35 (1H, d, J=3.0Hz), 10.6 (1H, s), 10.8 (1H, s). MS(ESI) m/z 476$(M+H)^+$.

(Example 27)

According to the same method as that used in the process 2 of example 1, a compound of example 27 was synthesized by using 2-methyl-cyclopropanecarbonylchloride as a starting material.

1H-NMR (300MHz, DMSO-d6) δ =0.58-0.66 (2H, m), 0.76-1.00 (2H, m), 1.07 (3H, s), 1.08 (3H, s), 1.16-1.22 (2H, m), 1.45-1.49 (2H, m), 6.91 (1H, d, J=8.7Hz), 6.98 (2H, d, J=9.0Hz), 7.54 (2H, d, J=8.7Hz), 7.99 (1H, dd, J=2.7, 9.0Hz), 8.26 (1H, d, J=2.7Hz), 8.26 (1H, d, J=2.7Hz), 10.1 (1H, s), 10.2 (1H, s). MS(ESI) m/z 366$(M+H)^+$, 364$(M-H)^-$.

(Example 28)

According to the same method as that used in the process 2 of example 1, a compound of example 28 was synthesized by using cyclohexane- carbonylchloride as a starting material.

1H-NMR (300MHz, DMSO-d6) δ =1.17-1.14 (10H, m), 1.66-1.82 (10H, m), 2.31 (2H, br), 6.93 (1H, d, J=8.7Hz), 6.99 (2H, d, J=8.7Hz), 7.59 (2H, d, J=8.7Hz), 8.04 (1H, dd, J=3.0, 8.7Hz), 8.30 (1H, d, J=3.0Hz), 9.80 (1H, s), 9.93 (1H, s). MS(ESI) m/z 422$(M+H)^+$.

(Example 29)

According to the same method as that used in the process 2 of example 1, a compound of example 29 was synthesized by using 2-methyl-cyclohexanecarbonylchloride as a starting material.

1H-NMR (300MHz, DMSO-d6) δ =0.82-0.90 (6H, m), 1.29-1.51 (12H, m), 1.64-1.69 (4H, m), 2.12 (2H, brs), 2.49-2.53 (2H, m), 6.93 (1H, d, J=8.7Hz), 6.99 (2H, d, J=8.7Hz), 7.59 (2H, d, J=8.7Hz), 8.04 (1H, dd, J=3.0, 8.7Hz), 8.30 (1H, d, J=3.0Hz), 9.74 (1H, s), 9.86 (1H, s). MS(ESI) m/z 450 $(M+H)^+$.

(Example 30)

According to the same method as that used in the process 2 of example 1, a compound of example 30 was synthesized by using 3-cyclohexane-carbonylchloride as a starting material.

1H-NMR (300MHz, DMSO-d6) δ =1.55-1.62 (2H, m), 1.90 (2H, d, J=12Hz), 2.13 (8H, d, J=14Hz), 2.49-2.55 (4H, m), 6.95 (1H, d, J=8.7Hz), 7.01 (2H, d, J=8.7Hz), 7.61 (2H, d, J=8.7Hz), 8.05 (1H, dd, J=3.0, 8.7Hz), 8.33 (1H, d, J=3.0Hz), 9.91 (1H, s), 10.0 (1H, s). MS(ESI) m/z 418$(M+H)^+$.

(Example 31)

Process 1:

Sodium hydroxide (10g) was dissolved into a mixed solution of water (100ml) and dioxane (100ml), which was added with 4-hydroxyaniline (10.9g, 0.1mol) under the ice water cooling and further added slowly with Boc_2O (27.3g, 0.125mmol), and then stirred at 0℃ for 4 hours. After the reaction having been completed, the solvent was evapolated, and the resultant was neutralized with aqueous solution of ammonium chloride, extracted with ethyl acetate, and after having been washed, dried and concentrated according to the conventional manner, then purified by way of the silica gel chromatography (ethyl acetate, hexane), thus obtained the objective 4-t-butoxycarbonylaminophenol (37) in the form of a white crystal (12.3g, 58%).

1H-NMR (300MHz, $CDCl_3$) δ =1.53 (9H, s), 5.30 (1H, brs), 6.35 (1H, brs), 6.73 (2H, d, J=8.7Hz), 7.15 (2H, d, J=8.7Hz).

Process 2:

The 4-t-butoxycarbonylaminophenol (37) (8.36g, 40mmol) obtained in the process 1, the 2-chloro-5-nitropyridine (36) (6.24, 40mmol) and potassium carbonate (11.4g, 80mmol) were stirred in the dimethylformamide (100ml) at 80℃ for 3 hours. After the reaction having been completed, the solvent was evaporated and the resultant was extracted with ethyl acetate, and after having been washed, dried and concentrated according to the conventional manner, then crystallized again with a mixed solvent of ethanol and ethyl acetate, thus obtained an objective ether compound (38) in the form of a yellow crystal (11.88g, 90%).

1H-NMR (300MHz, $CDCl_3$) δ =1.55 (9H, s), 6.54 (1H, brs), 7.01 (1H, d, J=8.5Hz), 7.10 (2H, d, J=8.7Hz), 7.45 (2H, d, J=8.7Hz), 8.47 (1H, dd, J=8.5, 2.5Hz), 9.04 (1H, d, J=2.5Hz).

Process 3:

A mixed solvent of the ether compound (38) (2g, 6.6mmol) obtained in the process 2 mixed with ethanol (50ml) and dioxane (20ml) was added with 10%-palladium carbon (1g) and reduced under the hydrogen pressure of 5 atmosphere at the room temperature for 15 hours. After the reaction having been completed, the solid matter was filtered out, and the filtrate was purified by way of the silica gel chromatography (ethyl acetate, hexane), thus obtained objective compound in the reduced form (39) (1.90g, 93%).

1H-NMR (300MHz, $CDCl_3$) δ =1.55 (9H, brs), 6.44 (1H, brs), 6.74 (1H, d, J=8.5Hz), 7.01 (2H, d, J=8.7Hz), 7.06 (1H, dd, J=8.5, 3.0Hz), 7.34 (2H, d, J=8.7Hz), 7.70 (1H, d, J=3.0Hz).

Process 4:

A dichloromethane (100ml) solution of the reduced form (39) (1.6g, 5.3mmol) obtained in the process 3 and triethylamine (2g, 20mmol) was added with dichloromethane (10ml) solution of 2,2-dimethylcyclopropanecarbonylchloride (1.05mg, 8mmol), which was in turn stirred at the room temperature for 4 hours.

After the reaction having been completed, the solvent was distilled out under reduced-pressure condition and the resultant was extracted with ethyl acetate, and after having been washed, dried and concentrated according to the conventional manner, then the resultant was purified by way of the silica gel chromatography (ethyl acetate, hexane), thus obtained an objective amide compound (40:R2= 2,2-dimethylcyclopropane) in the form of a white crystal (1.95g, 67%).

1H-NMR (300MHz, DMSO-d6) δ =0.76-0.83 (1H, m), 0.95-1.02 (1H, m), 1.17 (3H, s), 1.19 (3H, s), 1.55 (9H, brs), 1.60-1.66 (1H, m), 6.92 (1H, d, J=9.1Hz), 6.99 (2H, d, J=8.7Hz), 7.44 (2H, d, J=8.7Hz), 8.03 (1H, dd, J=9.1, 3.8Hz), 8.30 (1H, d, J=3.8Hz), 9.33 (1H, s), 10.20 (1H, s).

Process 5:

An ethanol (50ml) solution of the amide compound (40:R2= 2,2-dimethylcyclopropane) (8g, 20mmol) obtained in the process 4 was added with 4M hydrochloric acid-dioxane solution (20ml) and stirred at the room temperature for 20 hours. After the reaction having been completed, the solvent was distilled out under reduced-pressure condition, and then dimethyl ether (50ml) was added into the resultant to be crystallized, thus obtained an objective hydrochloride of the amine body (41:R2= 2,2-dimethylcyclopropane) in the form of a brown crystal (7.24g, yield of 98% as 2hydrochloride).

1H-NMR (300MHz, DMSO-d6) δ =0.78 (1H, dd, J=7.8, 3.9Hz), 0.94-0.98 (1H, m), 1.12 (3H, s), 1.14 (3H, s), 1.66 (1H, dd, J=7.8, 5.1Hz), 7.03 (1H, d, J=9.0Hz), 7.18 (2H, d, J=8.7Hz), 7.40 (2H, d, J=8.7Hz), 8.09 (1H, dd, J=8.7, 2.7Hz), 8.34 (1H, d, J=2.7Hz), 10.00-10.06 (2H, br), 10.36 (1H, s).

Process 6:

A methylene chloride solution (10ml) of the hydrochloride (111mg, 0.33mmlo) of the amine compound (41:R2= 2,2-dimethylcyclopropane) obtained in

the process 5 was added with triethylamine (202mg, 2.0mmol) and cooled in the ice bath, into which the methylene chloride solution (5ml) of benzoylchloride (72mg, 0.51mmol) was dropped. After the reaction was completed, the resultant was concentrated, extracted with methylene chloride, and after having been washed, dried and concentrated according to the conventional manner, then purified by way of the silica gel column chromatography (methylene chloride, methanol), thus obtained a compound of example 31 (117mg).

H-NMR (300MHz, DMSO-d6) δ =0.79-0.83 (1H, m), 0.99 (1H, t, J=4.5Hz), 1.16 (6H, d, J=6.5Hz), 1.66 (1H, t, 6.5Hz), 6.97 (1H, d, J=9.2Hz), 7.08 (2H, dd, J=2.1, 6.5Hz), 7.51-7.60 (3H, m), 7.77 (2H, dd, J-2.1, 6.5Hz), 8.07 (1H, dd, J=2.7, 9.2Hz), 8.32 (1H, d, J=2.7Hz), 10.2 (1H, s), 10.4 (1H, s). MS(ESI) m/z 402$(M+H)^+$.

(Example 32)

According to the same method as of the process 6 of example 31, a compound of example 32 was synthesized by using phenyl-acetylchloride and the hydrochloride of the amine compound (41) obtained in the process 5 of example 31 as a starting material.

1H-NMR (300MHz, DMSO-d6) δ =0.79-0.83 (1H, m), 0.99 (1H, t, J=4.5Hz), 1.16 (6H, d, J=6.5Hz), 1.66 (1H, t, J=6.5Hz), 3.62 (1H, s), 6.91 (1H, d, J=9.2Hz), 7.02 (2H, d, J=6.5Hz), 7.21-7.37 (5H, m), 7.59 (2H, d, 6.5Hz), 8.04 (1H, dd, J=2.7, 9.2Hz), 8.30 (1H, d, J=2.7Hz), 10.2 (2H, d, 6.0Hz). MS(ESI) m/z 416$(M+H)^+$.

(Example 33)

According to the same method as of the process 6 of example 31, a compound of example 33 was synthesized by using 4-chlorophenylacetylchloride and the hydrochloride of the amine body (41) obtained in the process 5 of example 31 as a starting material.

1H-NMR (300MHz, DMSO-d6) δ =0.76-0.83 (1H, m), 0.95-1.02 (1H, m), 1.17 (3H, s), 1.19 (3H, s), 1.60-1.66 (1H, m), 3.65 (2H, s), 6.94 (1H, d, J=9.1Hz), 7.03 (2H, d,

J=8.7Hz), 7.34-7.42 (4H, m), 7.59 (2H, d, J=8.7Hz), 8.05 (1H, dd, J=9.1, 3.8Hz), 8.30 (1H, d, J=3.8Hz), 10.20 (1H, s). MS(ESI) m/z 450$(M+H)^+$.

(Example 34)

According to the same method as of the process 6 of example 31, a compound of example 34 was synthesized by using 4-methoxyphenyl-acethylchrolide and the hydrochloride (41) obtained in the process 5 of example 31 as a starting material.

1H-NMR (300MHz, $CDCl_3$) δ =0.72-0.76 (1H, m), 1.17-1.22 (7H, m), 1.38-1.49 (1H, m), 3.69 (2H, s), 3.81 (3H, s), 6.79-6.90 (4H, m), 6.99 (2H, d, J=8.7Hz), 7.26-7.33 (2H, m), 7.40 (2H, d, J=8.7Hz), 7.64 (1H, s), 8.06 (1H, s). MS(ESI) m/z 446$(M+H)^+$.

(Example 35)

According to the same method as of the process 6 of example 31, a compound of example 35 was synthesized by using 3,4-dimethoxy-phenylacethylchrolide and the hydrochloride (41) obtained in the process 5 of example 31 as a starting material.

1H-NMR (300MHz, DMSO-d6) δ =0.79-0.83 (1H, m), 0.989 (1H, t, J=4.5Hz), 1.16 (6H, d, J=6.5Hz), 1.66 (1H, t, 6.5Hz), 3.55 (2H, s), 3.62 (3H, s), 3.77 (6H, s), 6.65 (2H, s), 6.93 (1H, d, J=9.2Hz), 7.02 (2H, dd, J=2.1, 6.5Hz), 7.60 (2H, d, J=6.5Hz), 8.04 (1H, dd, J=2.7, 9.2Hz), 8.30 (1H, d, J=2.7Hz), 10.2 (1H, s), 10.4 (1H, s). MS(ESI) m/z 506$(M+H)^+$.

(Example 36)

According to the same method as of the process 6 of example 31, a compound of example 36 was synthesized by using 3,4,5-trimethoxy-phenylacethylchrolide and the hydrochloride (41) obtained in the process 5 of example 31 as a starting material.

1H-NMR (300MHz, DMSO-d6) δ =0.79-0.83 (1H, m), 0.989 (1H, t, J=4.5Hz), 1.16

(6H, d, J=6.5Hz), 1.66 (1H, t, 6.5Hz), 3.55 (2H, s), 3.71 (6H, d, J=6.0Hz), 6.83-6.95 (5H, m), 7.02(2H, d, J=9.2Hz), 7.59 (2H, d, J=9.2Hz), 8.04 (1H, dd, J=2.7, 9.0Hz), 8.30 (1H, d, J=2.7Hz), 10.1 (1H, s), 10.2 (1H, s). MS(ESI) m/z 476$(M+H)^+$.

(Example 37)

A methylene chloride solution (10ml) of the hydrochloride (254mg, 0.76mmol) of the amine compound (41) obtained in the process 5 of example 31 was added with triethylamine by 0.15ml and cooled in the ice bath, which was in turn further added with 4-phenylbutyric acid (144mg, 0.88mmol), WSC · HCl (173mg, 0.90mmol) and stirred over night. After the reaction having been completed, the resultant was concentrated and separately purified by way of the silica gel chromatography, thus obtained a compound (277mg) of example 37.

1H-NMR (300MHz, DMSO-d6) δ =0.79-0.83 (1H, m), 0.989 (1H, t, J=4.5Hz), 1.16 (6H, d, J=6.5Hz), 1.66 (1H, t, J=6.5Hz), 1.86-1.95 (2H, m), 2.32 (2H, t, J=7.5Hz), 2.63 (2H, t, J=7.5Hz), 6.94 (1H, d, J=9.0Hz), 7.01 (2H, dd, J=1.4Hz), 7.17-7.24 (5H, m), 8.05 (1H, d, J=9.0Hz), 8.30 (1H, s), 9.89 (1H, s), 10.2 (1H, s). MS(ESI) m/z 444$(M+H)^+$.

(Example 38)

A DMF solution (10ml) of the hydrochloride (120mg, 0.36mmol) of the amine compound (41) obtained in the process 5 of example 31 was added with triethylamine (50μ1, 0.36mmol), potassium carbonate (105mg, 0.76mmol), 2-buromoethylbenzene (58μ1, 0.43mmol) and sodium iodide (89mg, 0.59mol) to cause a reaction at 90℃. After the reaction was completed, the resultant was extracted with methylene chloride, and then washed with a saturated saline solution, dried and concentrated, and then purified by way of the silica gel thin layer chromatography. A 4M-HCl ethyl acetate solution was applied to this resultant in an ether solvent, thus obtained a compound (13mg) of example 38 as hydrochloride salt.

1H-NMR (300MHz, DMSO-D6) δ =0.78-0.84 (1H, m), 0.94-1.00 (1H, m), 1.15 (3H, s), 1.18 (3H, s), 1.63-1.68 (1H, m), 2.90-3.00(4H, m), 7.02 (1H, d, J=9.2Hz), 7.15 (2H, d, J=8.0Hz), 7.29-7.32 (7H, m), 8.09 (1H, d, J=9.2Hz), 8.36 (1H, d, J=2.8Hz), 10.7 (1H, s). MS(ESI) m/z 402$(M+H)^+$, 400$(M-H)^-$.

(Example 39)

According to the same method as of example 38, a compound of example 39 was synthesized by using 3-phenylpropylbromide and the hydrochloride of the amine compound (41) obtained in the process 5 of example 31 as a starting material.

1H-NMR (300MHz, DMSO-d6) δ =0.78-0.84 (1H, m), 0.94-1.00 (1H, m), 1.14 (3H, s), 1.16 (3H, s), 1.63-1.68 (1H, m), 1.92-2.00 (2H, m), 2.68-2.71 (2H, m), 3.21-3.28 (2H, m), 7.04 (1H, d, J=8.7Hz), 7.13-7.23 (5H, m), 7.29 (2H, d, J=7.0Hz), 7.46 (2H, d, J=7.0Hz), 8.10 (1H, d, J=2.8, 8.7Hz), 8.35 (1H, d, J=2.8Hz), 10.3 (1H, s). MS(ESI) m/z 416$(M+H)^+$, 414$(M-H)^-$.

(Example 40)

A dichloromethane solution (5ml) of the hydrochloride (111mg, 0.3mmol) of the amine compound (41) obtained in the process 5 of example 31 was added with triethylamine (101mg, 1mmol) and phenylisocyanate (60mg, 0.5mmol) and stirred at the room temperature for 20 hours. The generated precipitate was filtered to be taken, thus obtained a compound of example 40 (23mg, 18%) of a urea compound.

1H-NMR (300MHz, DMSO-d6) δ =0.76-0.82 (1H, m), 0.97-1.00 (1H, m), 1.14 (3H, s), 1.16 (3H, s), 1.62-1.66 (1H, m), 6.92-7.05 (4H, m), 7.28 (2H, t, J=8.7Hz), 7.45 (4H, d, J=8.7Hz), 8.05 (1H, dd, J=9.0, 2.7Hz), 8.30 (1H, d, J=2.4Hz), 8.64 (1H, s), 8.66 (1H, s), 10.20 (1H, s). MS(ESI) m/z 415$(M-H)^-$.

(Example 41)

A dichloromethane solution (5ml) of the hydrochloride (111mg, 0.3mmol) of

the amine compound (41) obtained in the process 5 of example 31 was added with triethylamine (101mg, 1mmol) and phenylisocyanate (68mg, 0.5mmol) and stirred at the room temperature for 20 hours. After the reaction was completed, the resultant was concentrated, extracted with methylene chloride, and after having been washed, dried and concentrated according to the conventional manner, further purified by way of the silica gel column chromatography (ethyl acetate, hexane), thus obtained a compound (83mg, 64%) of example 41.

1H-NMR (300MHz, DMSO-d6) δ =0.79-0.83 (1H, m), 0.97-1.00 (1H, m), 1.14 (3H, s), 1.17 (3H, s), 1.62-1.67 (1H, m), 6.98 (1H, d, J=8.7Hz), 7.05 (2H, d, J=8.7Hz), 7.13 (1H, t, J=7.5Hz), 7.33 (2H, t, J=8.1Hz), 7.45-7.51 (4H, m), 8.07 (1H, dd, J=8.7, 2.7Hz), 8.32 (1H, d, J=2.7Hz), 9.76 (2H, broad s), 10.22 (1H, s). MS(ESI) m/z 431$(M-H)^-$.

(Example 42)

A dichloromethane solution (5ml) of the hydrochloride (111mg, 0.3mmol) of the amine compound (41) obtained in the process 5 of example 31 was added with triethylamine (202mg, 2mmol) and benzenesulfonylchloride (88mg, 0.5mmol) and stirred at the room temperature for 20 hours. After the reaction having been completed, the resultant was concentrated, extracted with methylene chloride, and after having been washed, dried and concentrated according to the conventional manner, further purified by way of the silica gel column chromatography (ethyl acetate, hexane), thus obtained a compound (43mg, 33%) of example 42.

1H-NMR (300MHz, DMSO-d6) δ =0.78-0.82 (1H, m), 0.96-1.00 (1H, m), 1.13 (3H, s), 1.16 (3H, s), 1.61-1.66 (1H, m), 6.90-6.97 (3H, m), 7.06 (2H, d, J=8.4Hz), 7.50-7.65 (3H, m), 7.75 (2H, d, J=8.1Hz), 8.04 (1H, dd, J=9.0, 2.7Hz), 8.27 (1H, d, J=2.4Hz), 10.20 (2H, s). MS(ESI) m/z 438$(M+H)^+$.

(Example 43)

According to the same method as of example 1, and by using (S)-2,2-dimethylcyclopropanecarbonyl chloride in the process 2, a compound of example 43 was synthesized.

1H-NMR (300MHz, DMSO-d6) δ =0.75-0.83 (2H, m), 0.96-1.01 (2H, m), 1.13-1.18 (12H, m), 1.60-1.68 (2H, m), 6.93 (1H, d, J=8.7Hz), 7.00 (2H, d, J=8.7Hz), 7.60 (2H, d, J=8.7Hz), 8.05 (1H, dd, J=8.7, 2.7Hz), 8.31 (1H, d, J=2.7Hz), 10.07 (1H, s), 10.20 (1H, s). $[\alpha]D$=+123.7° (c=0.3, MeOH).

(Example 44)

According to the same method as of example 31, and by using (S)-2,2-dimethylcyclopropanecarbonyl chloride in the process 4 and further using (R)-2,2-dimethylcyclopropanecarbonyl chloride in the process 6, a compound of example 44 was synthesized.

1H-NMR (300MHz, DMSO-d6) δ =0.75-0.82 (2H, m), 0.96-1.01 (2H, m), 1.13-1.18 (12H, m), 1.61-1.68 (2H, m), 6.93 (1H, d, J-8.7Hz), 7.00 (2H, d, J=8.7Hz), 7.60 (2H, d, J=8.7Hz), 8.05 (1H, dd, J=8.7, 2.7Hz), 8.31 (1H, d, J=2.7Hz), 10.07 (1H, s), 10.21(1H, s).

(Example 45)

According to the same method as of example 31, and by using (R)-2,2-dimethylcyclopropanecarbonyl chloride in the process 4 and further using (S)-2,2-dimethylcyclopropanecarbonyl chloride in the process 6, a compound of example 45 was synthesized.

1H-NMR (300MHz, DMSO-d6) δ =0.75-0.82 (2H, m), 0.96-1.01 (2H, m), 1.13-1.18 (12H, m), 1.61-1.68 (2H, m), 6.93 (1H, d, J-8.7Hz), 7.00 (2H, d, J=8.7Hz), 7.60 (2H, d, J=8.7Hz), 8.05 (1H, dd, J=8.7, 2.7Hz), 8.30 (1H, d, J=2.7Hz), 10.07 (1H, s), 10.20 (1H, s).

(Example 46)

According to the same method as of example 1, and by using (R)-2,2-

dimethylcyclopropanecarbonylchloride in the process 2, a compound of example 46 was synthesized.

1H-NMR (300MHz, DMSO-d6) δ =0.75-0.82 (2H, m), 0.96-1.00 (2H, m), 1.13-1.18 (12H, m), 1.61-1.68 (2H, m), 6.92 (1H, d, J=8.7Hz), 6.98 (2H, d, J=8.7Hz), 7.58 (2H, d, J=8.7Hz), 8.03 (1H, dd, J=8.7, 2.7Hz), 8.29 (1H, d, J=2.7Hz), 10.06 (1H, s), 10.19 (1H, s). $[\alpha]$D=-146.5° (c=0.17, MeOH).

Those compounds synthesized in examples 1 to 46 are shown as follows:

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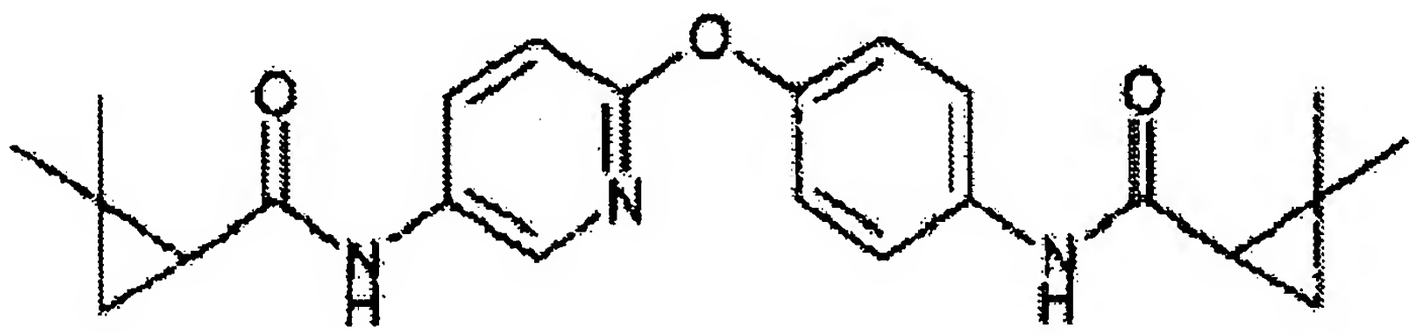
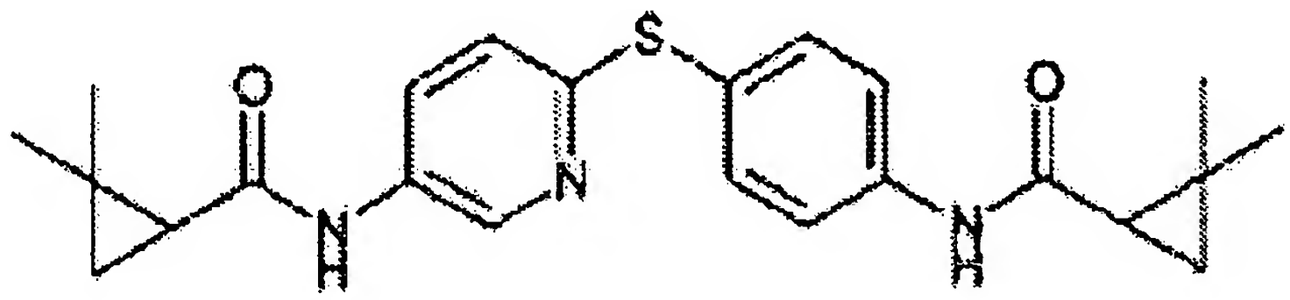
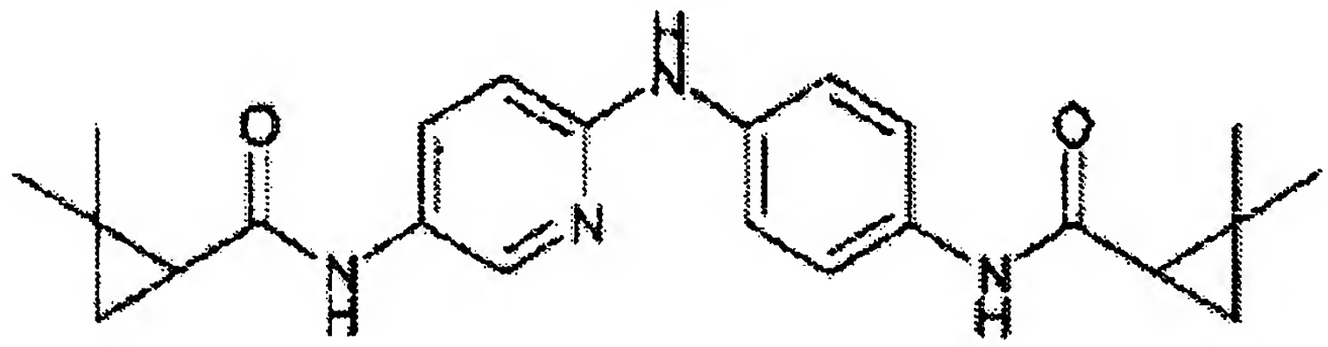
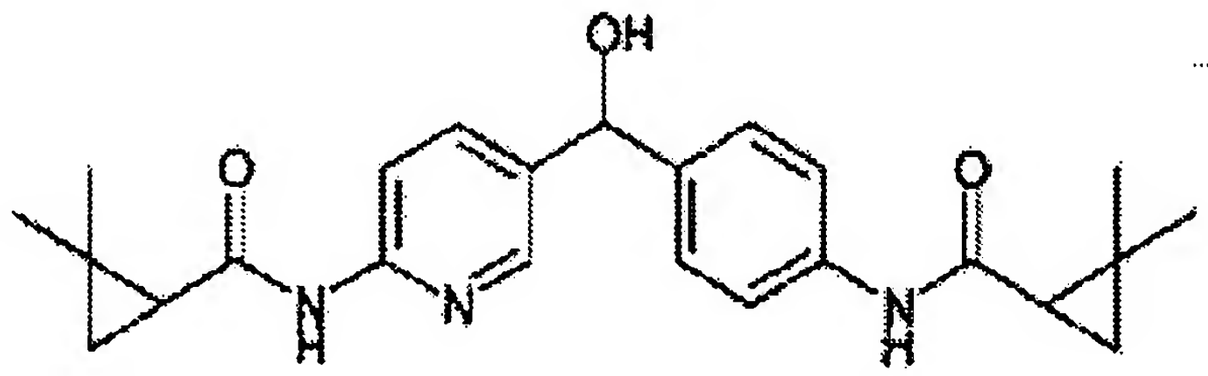
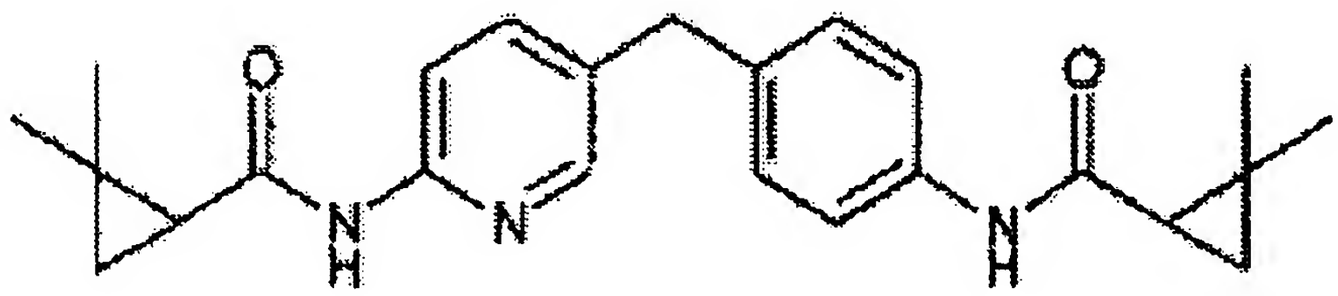
1	
2	
3	
4	
5	
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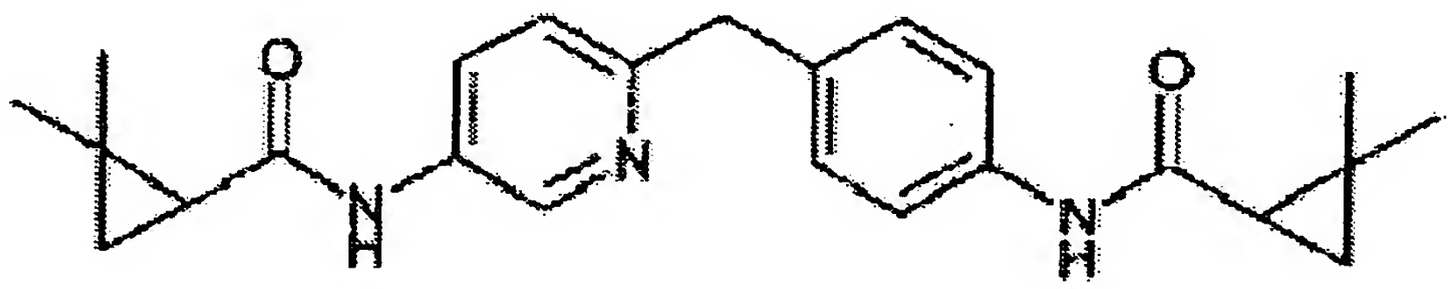
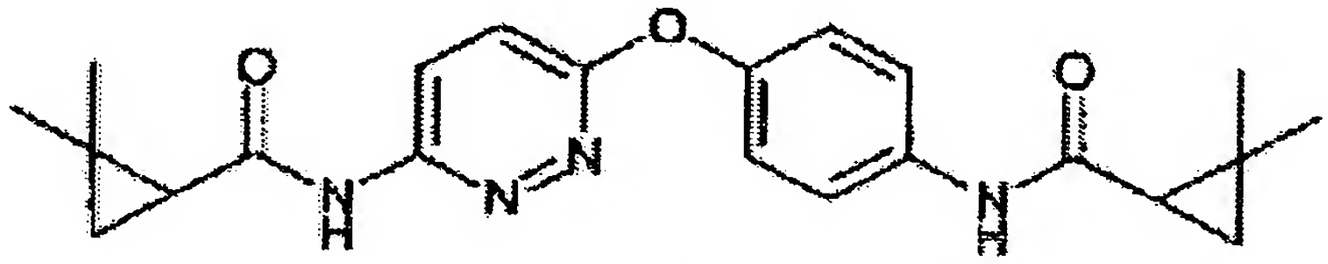
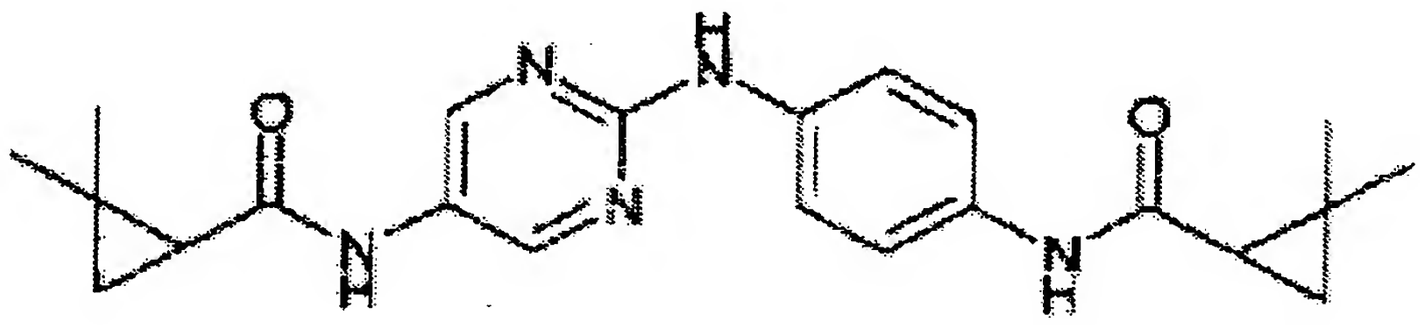
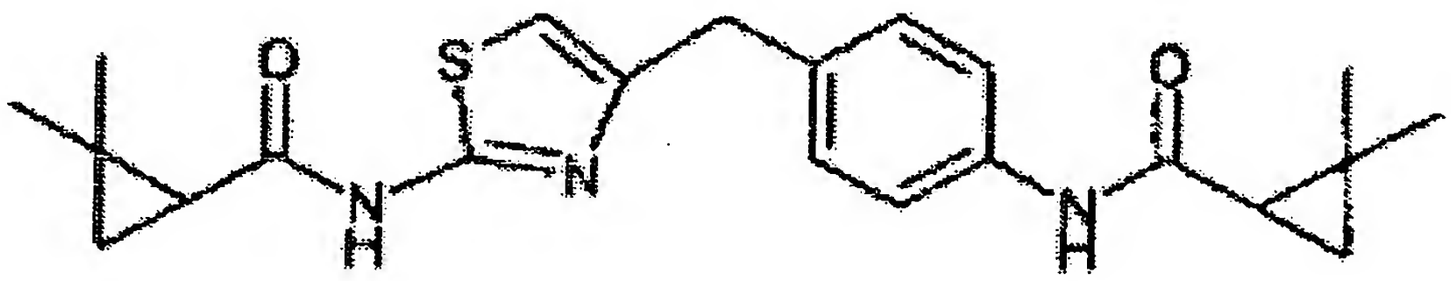
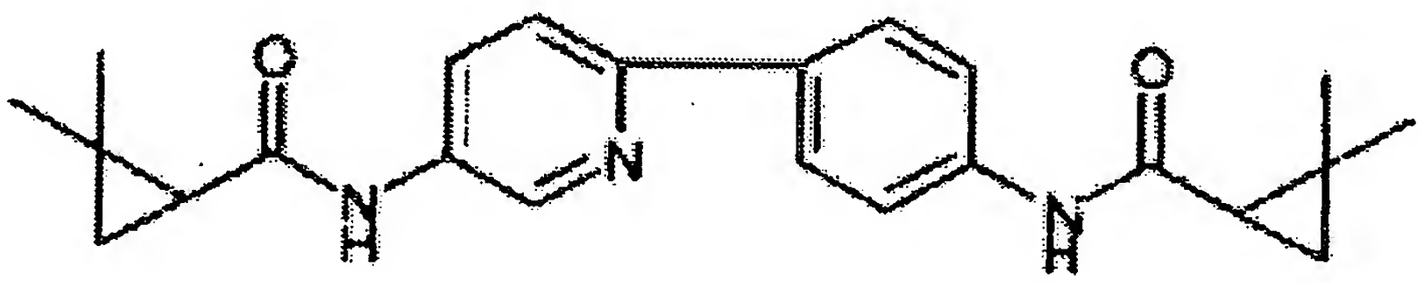
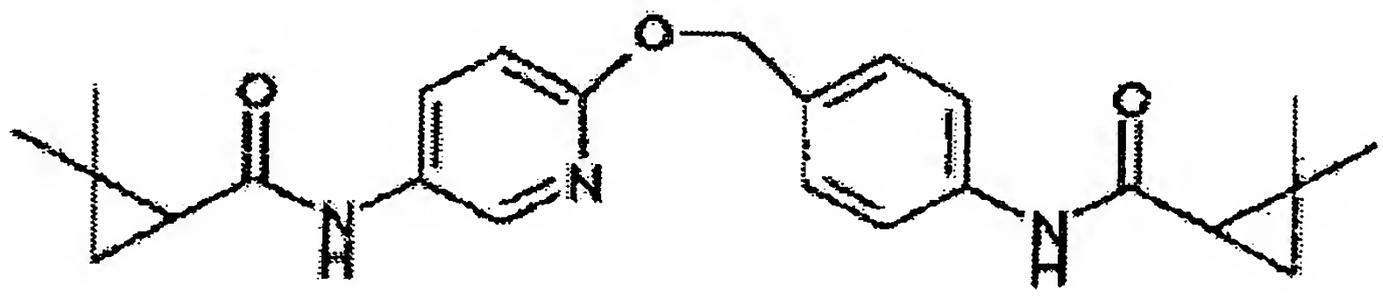
7	
8	
9	
10	
11	
12	

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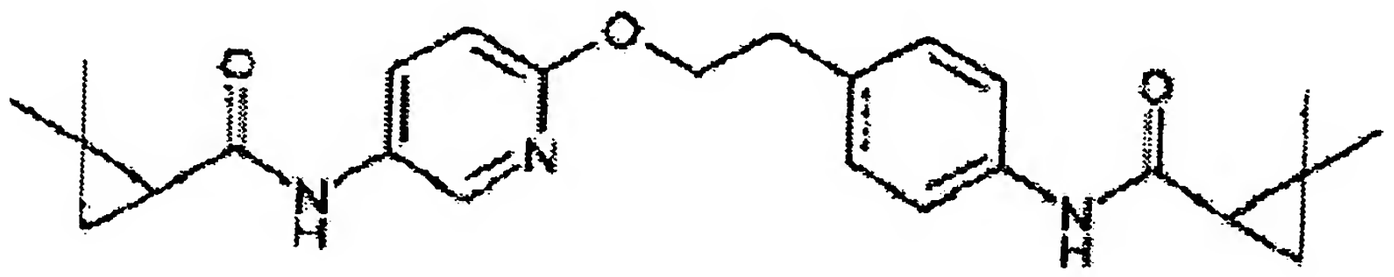
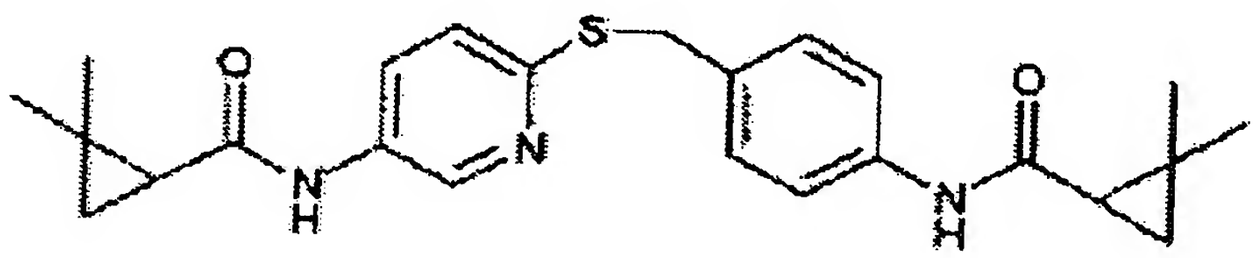
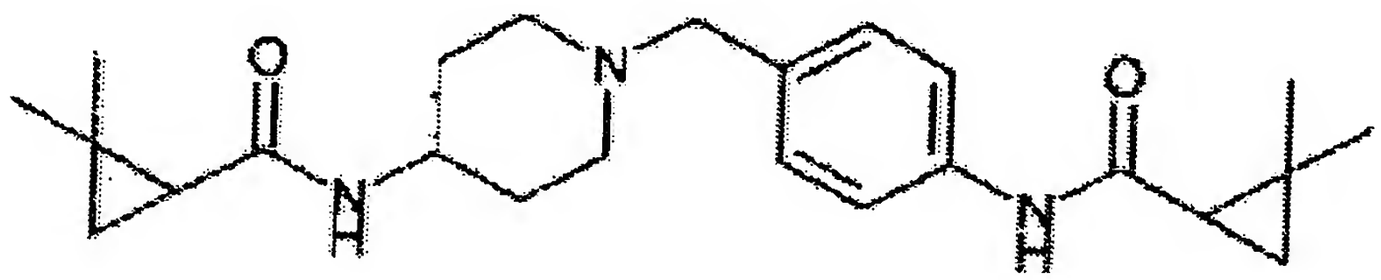
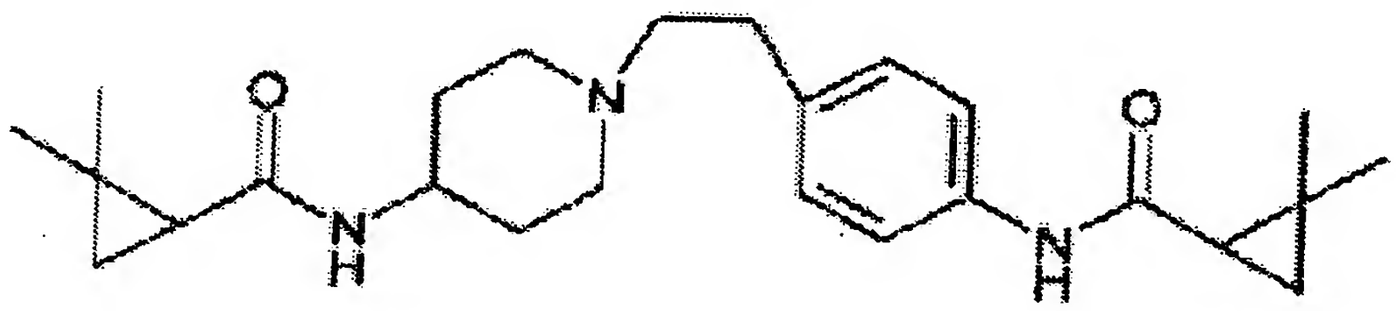
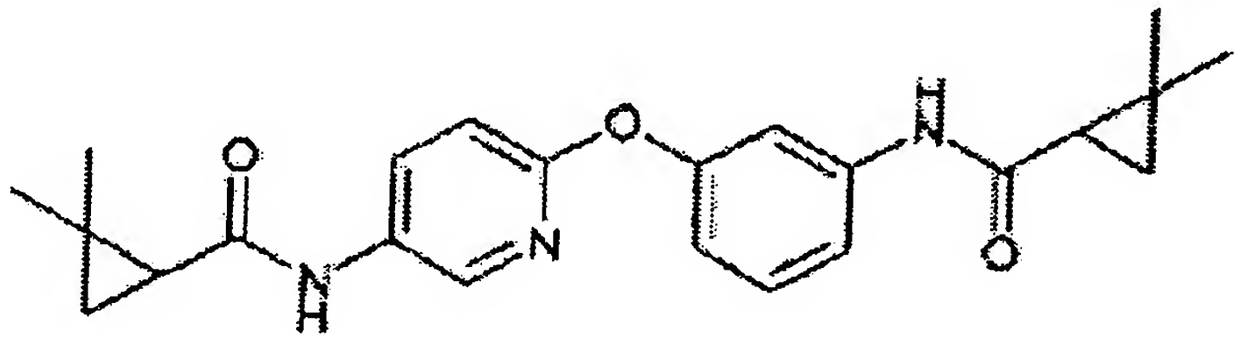
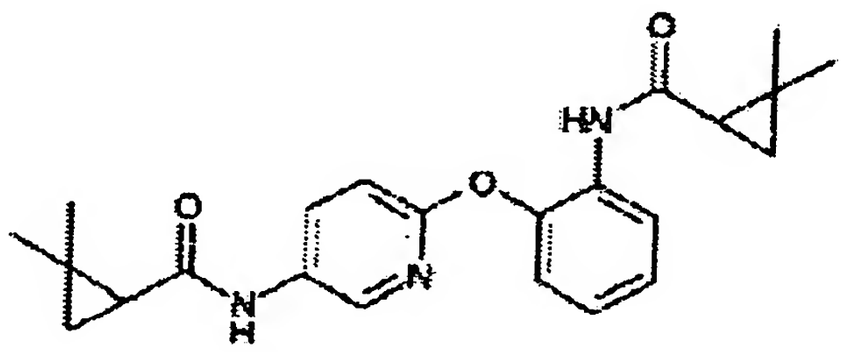
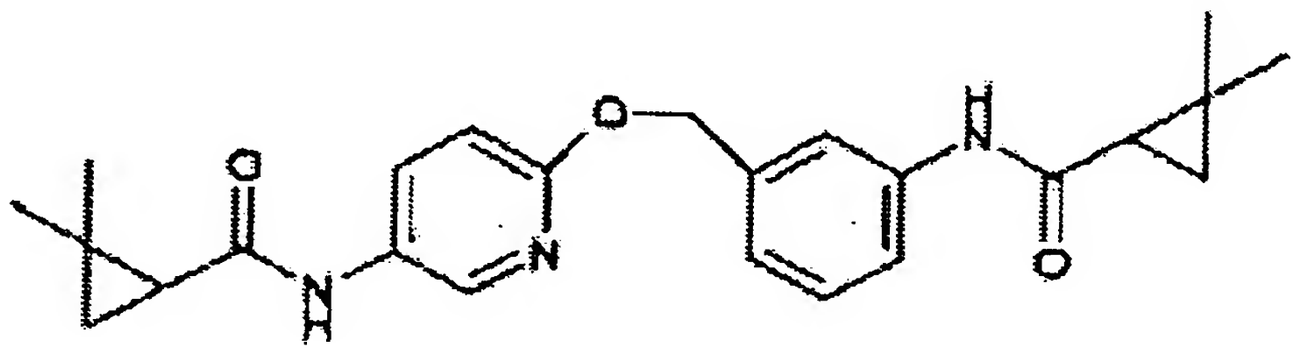
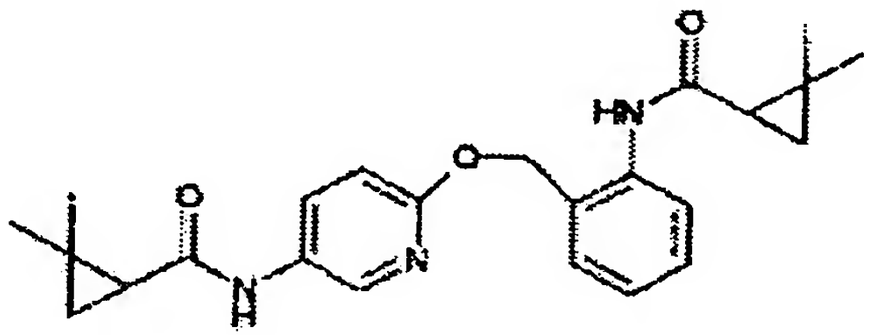
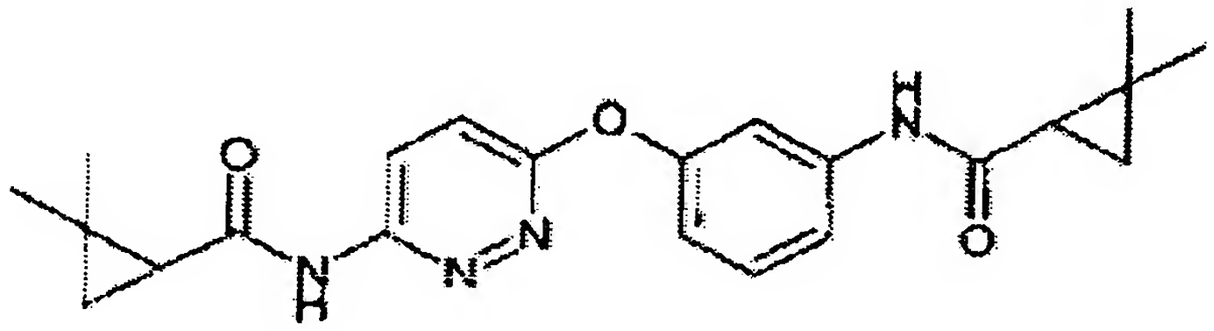
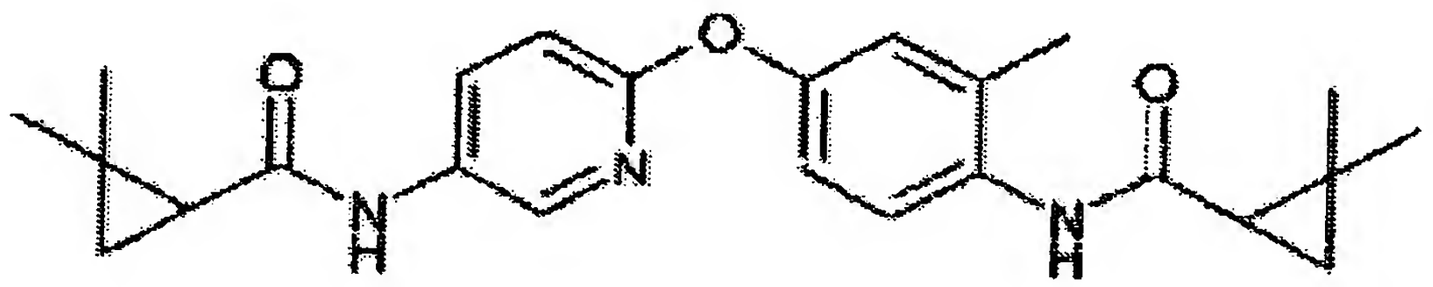
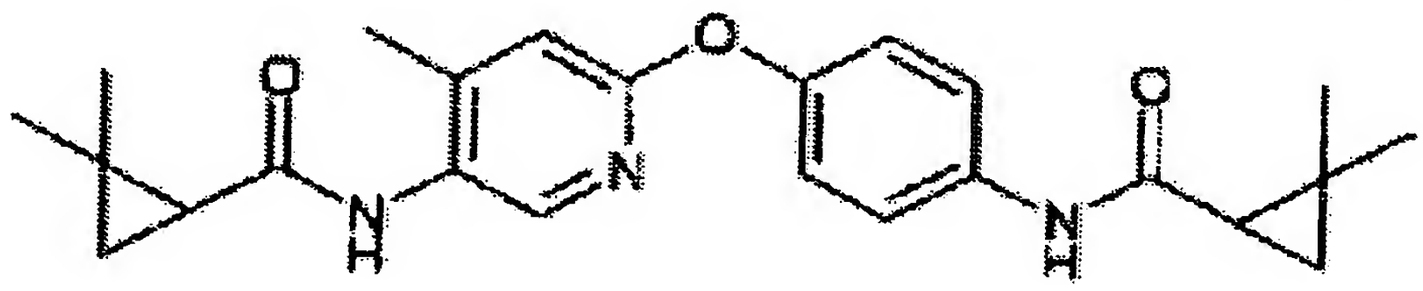
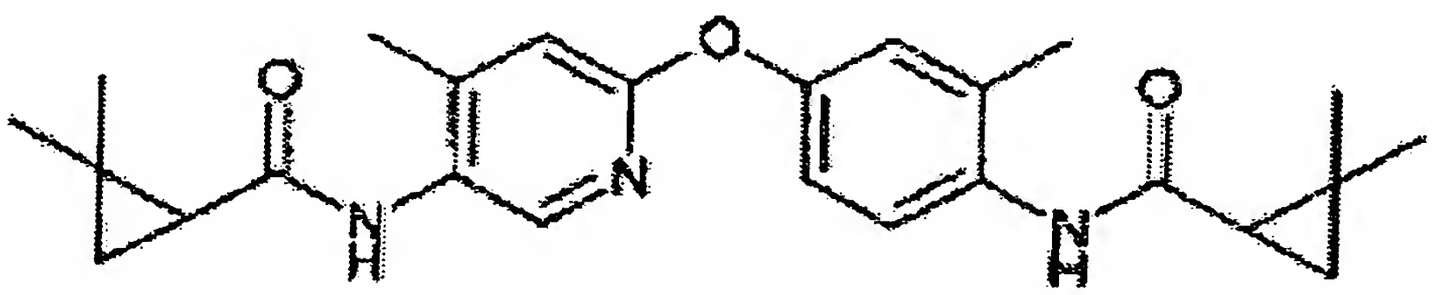
13	
14	
15	
16	
17	
18	

Example No.	structural formula
19	
20	
21	
22	
23	
24	

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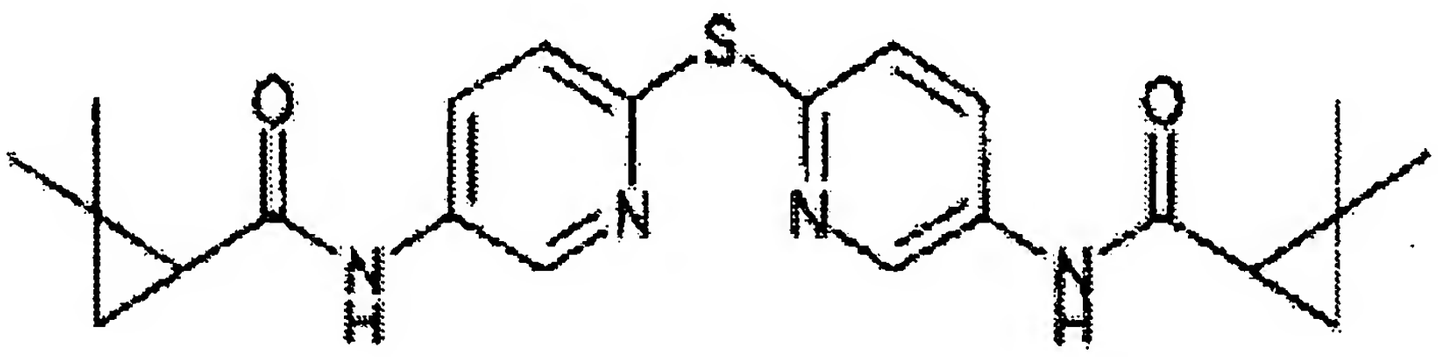
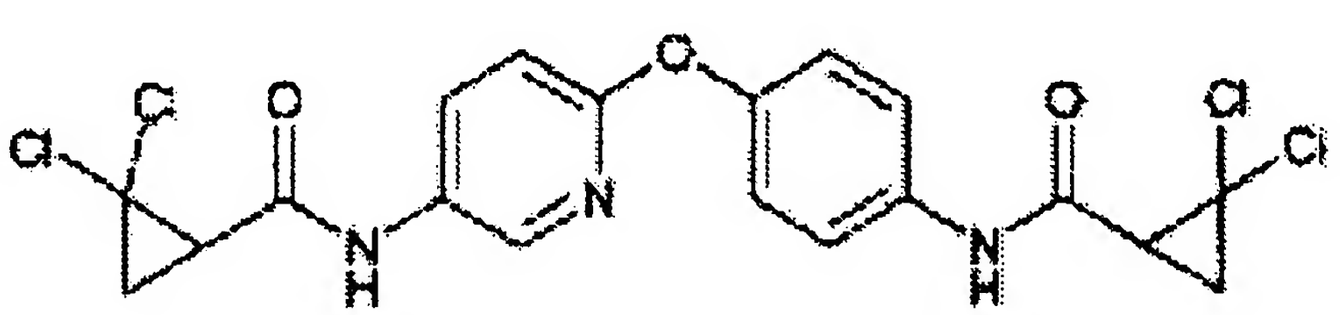
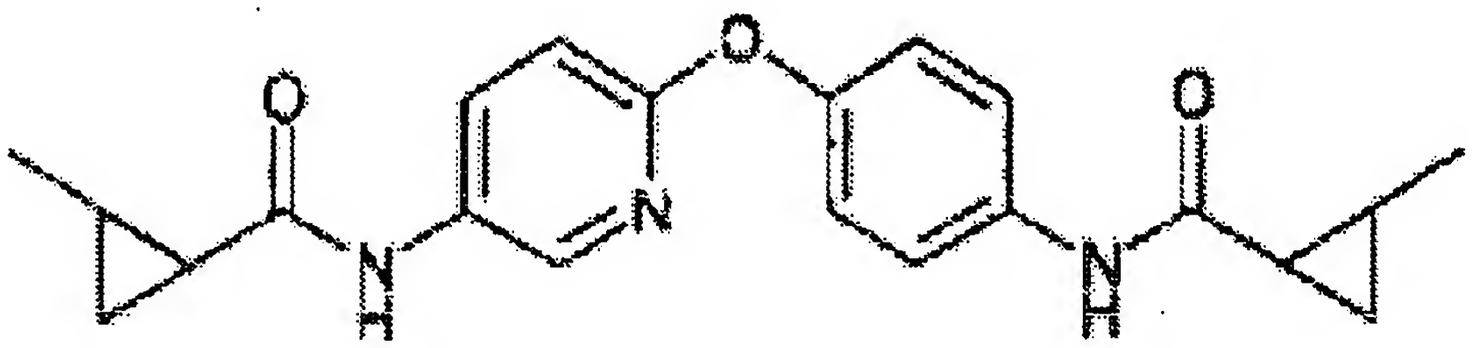
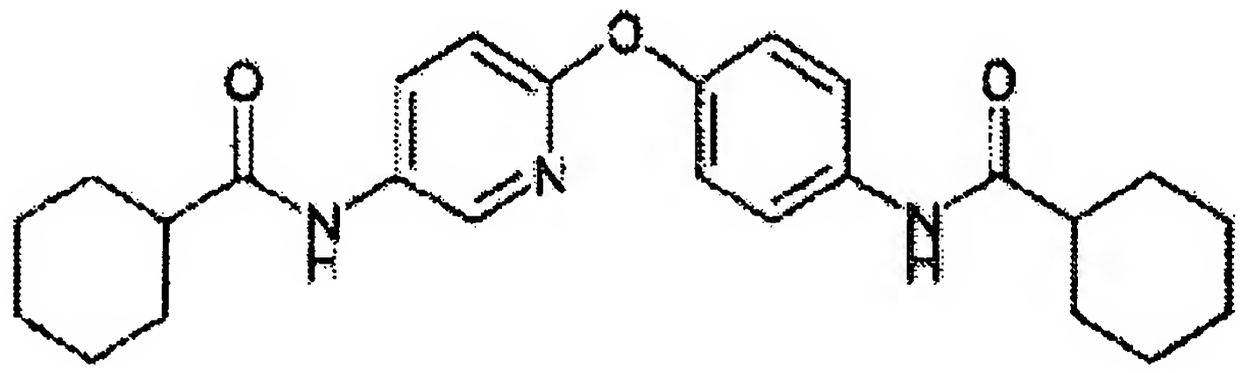
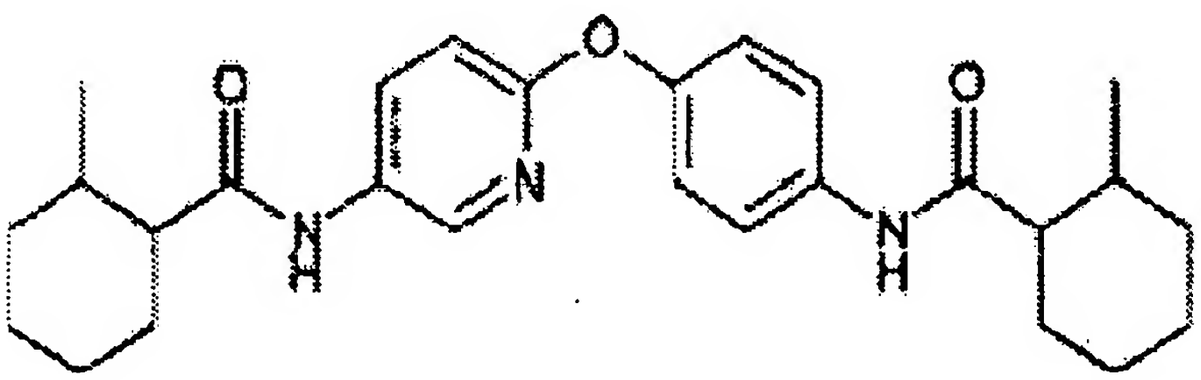
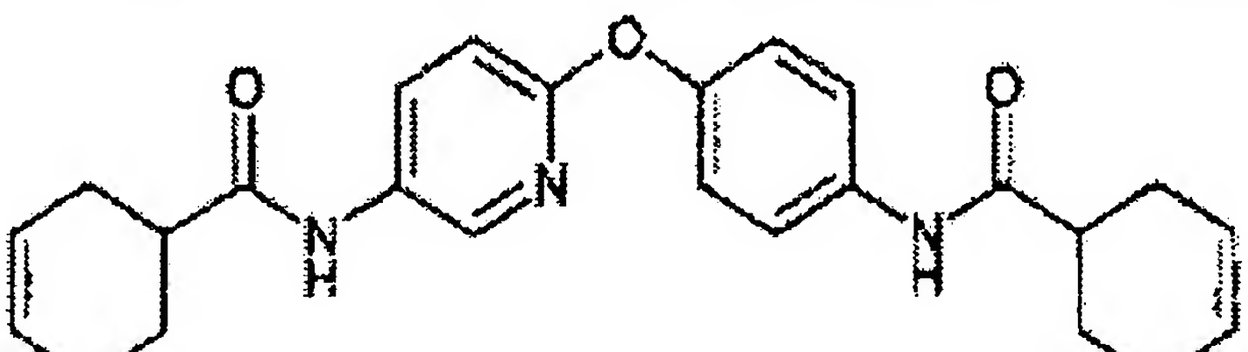
25	
26	
27	
28	
29	
30	

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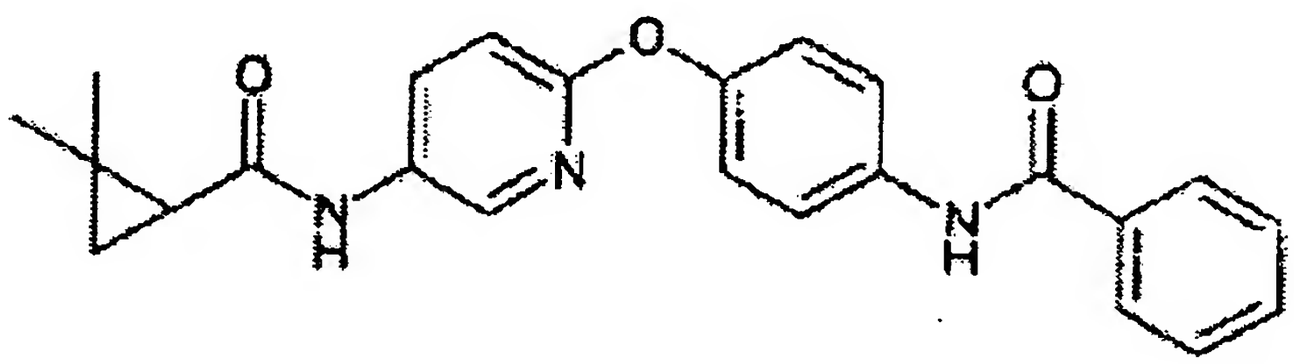
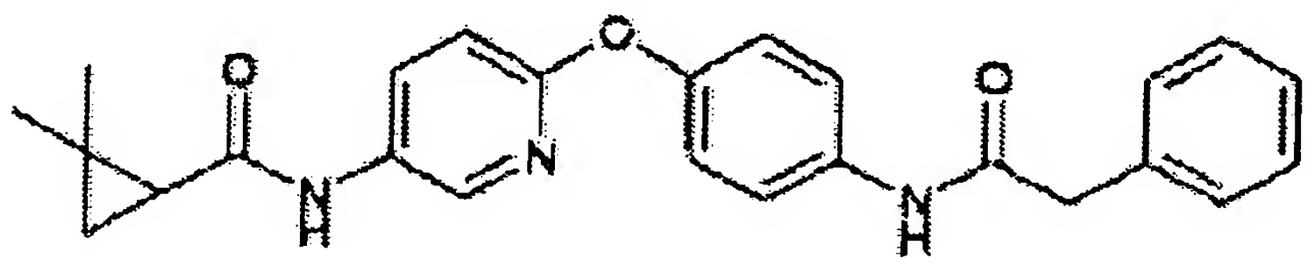
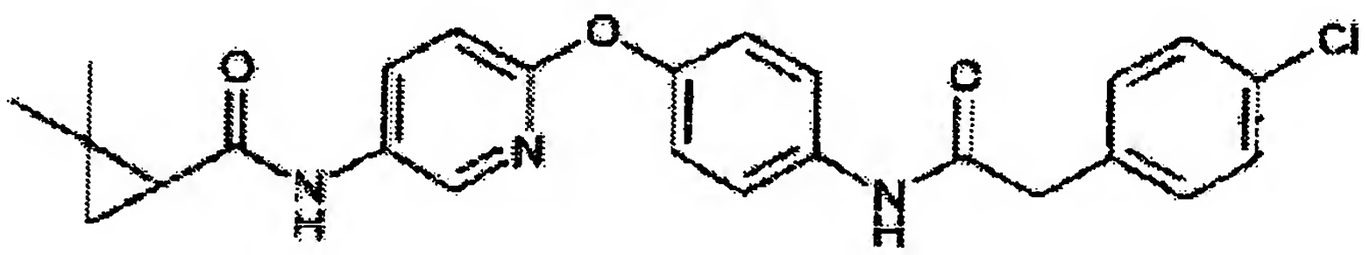
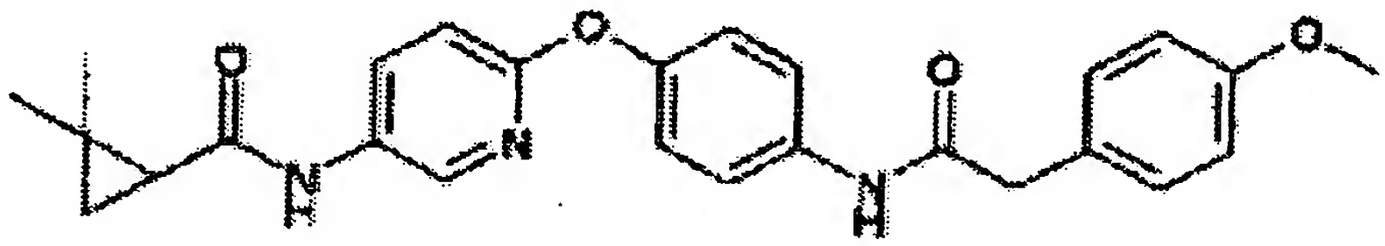
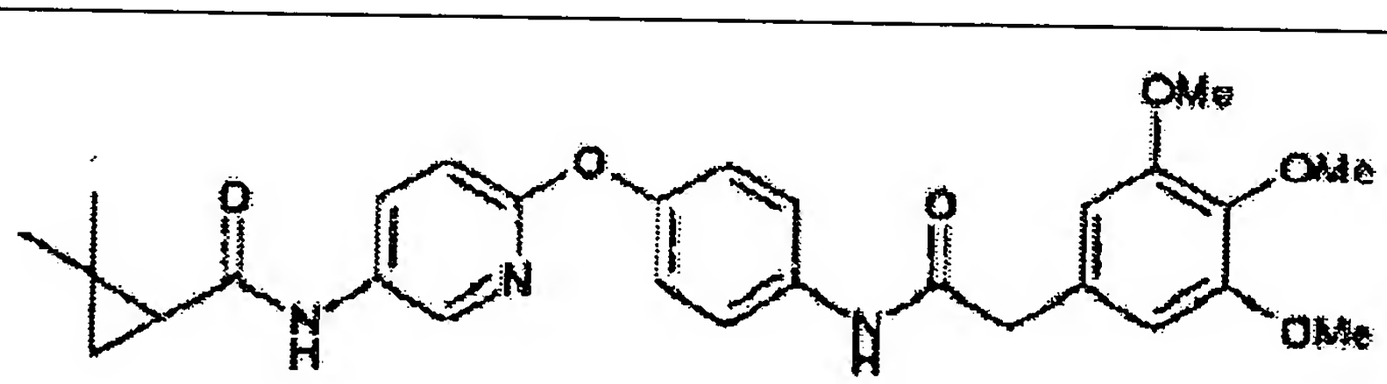
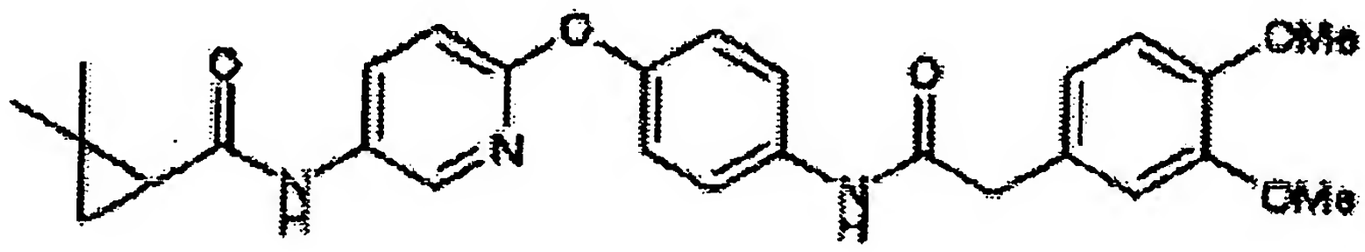
31	
32	
33	
34	
35	
36	

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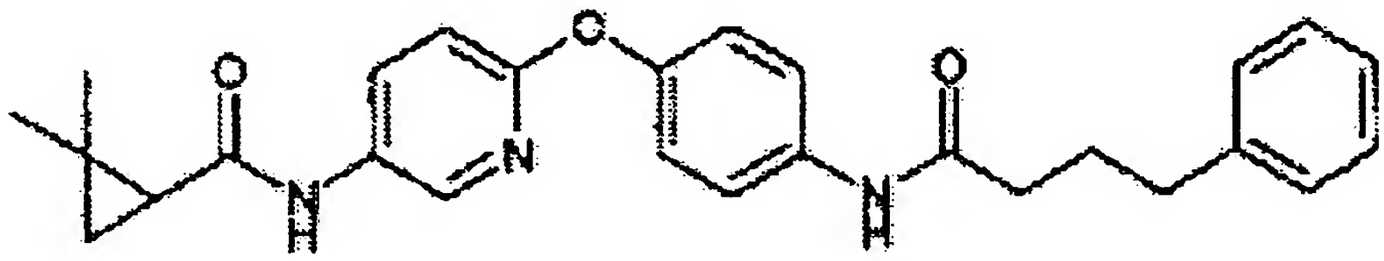
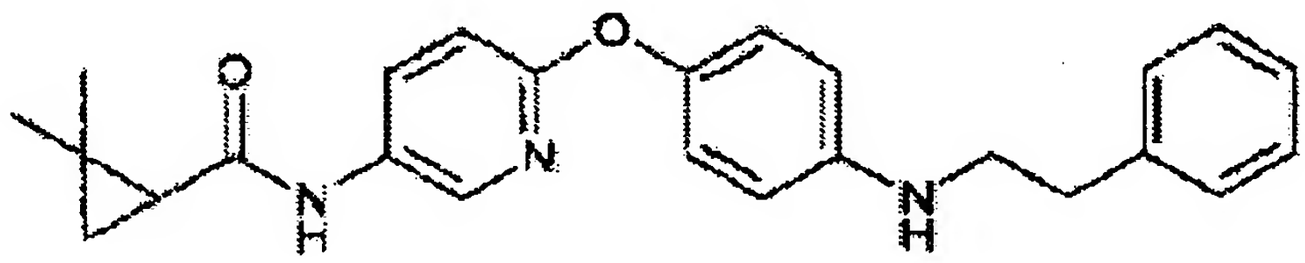
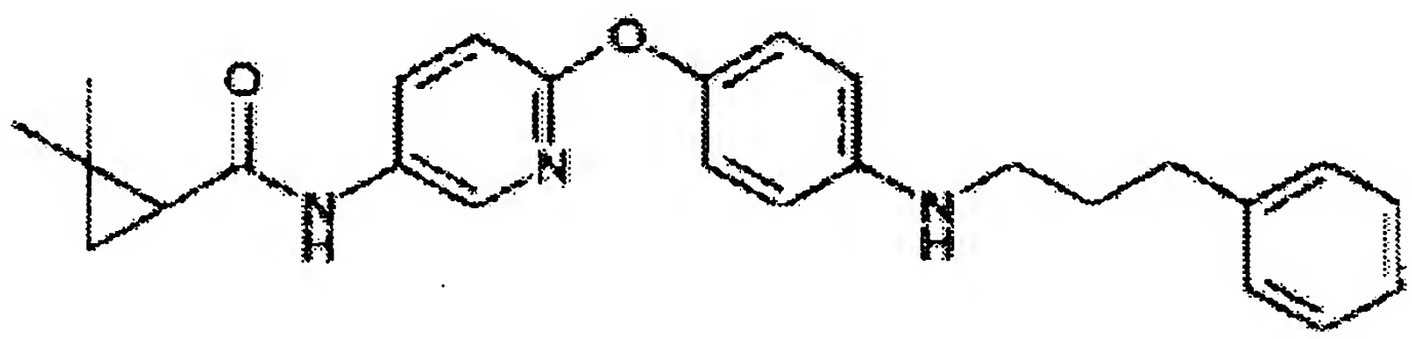
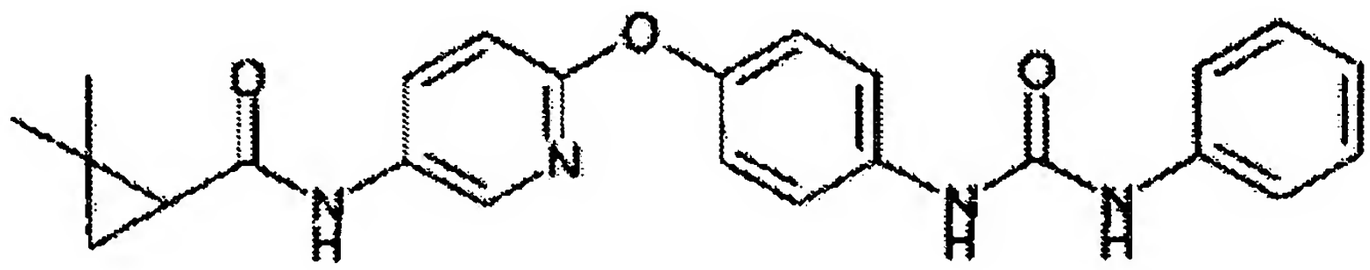
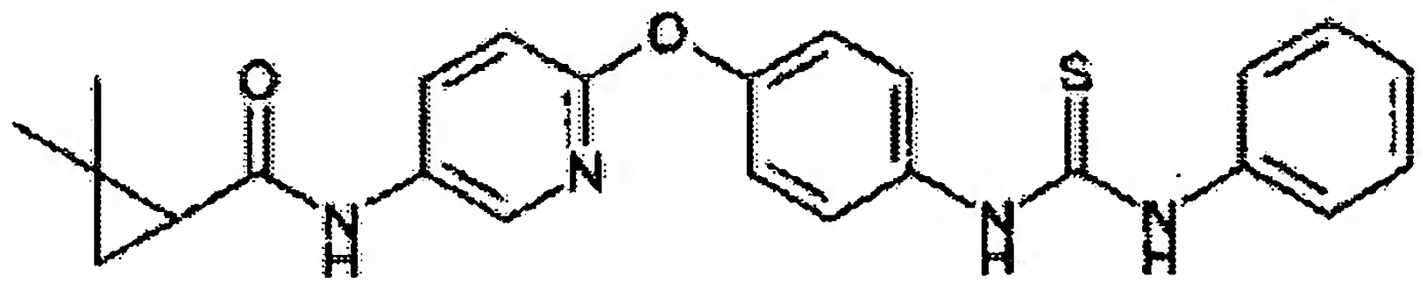
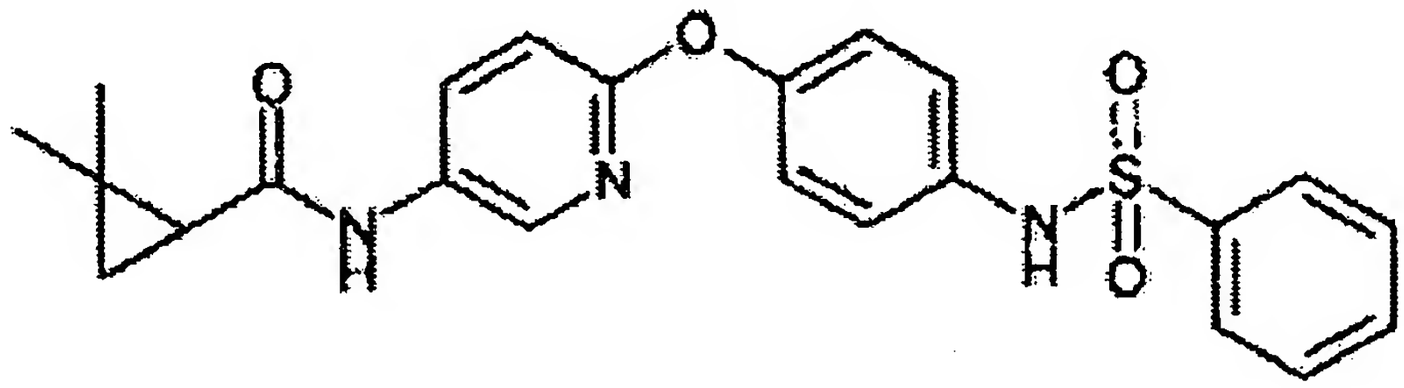
37	
38	
39	
40	
41	
42	

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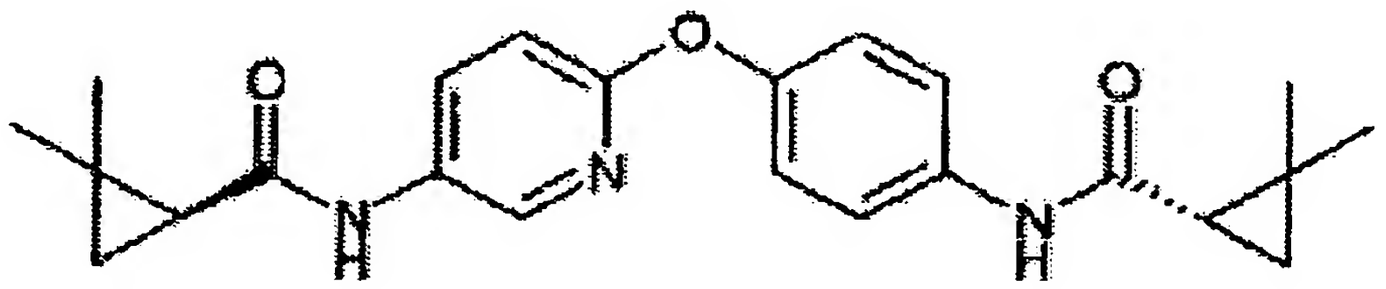
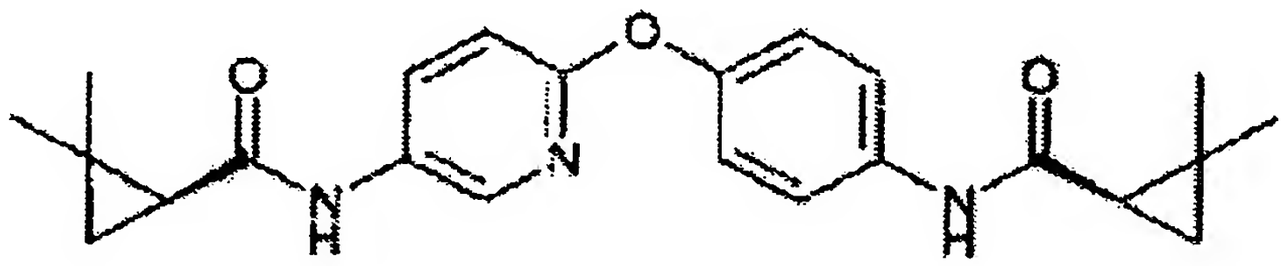
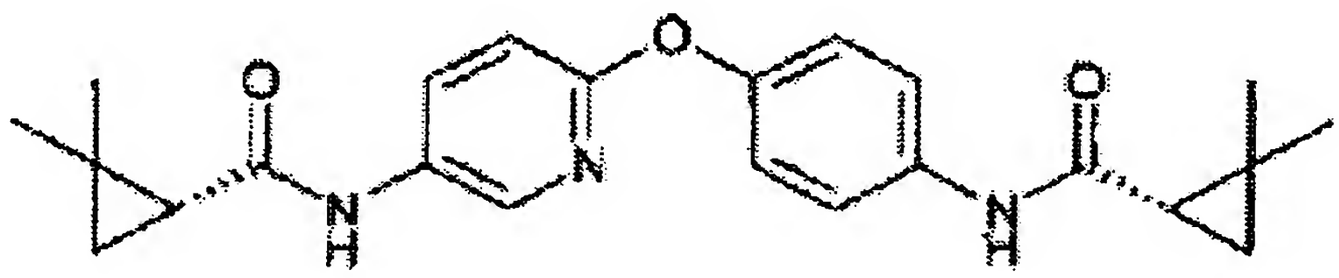
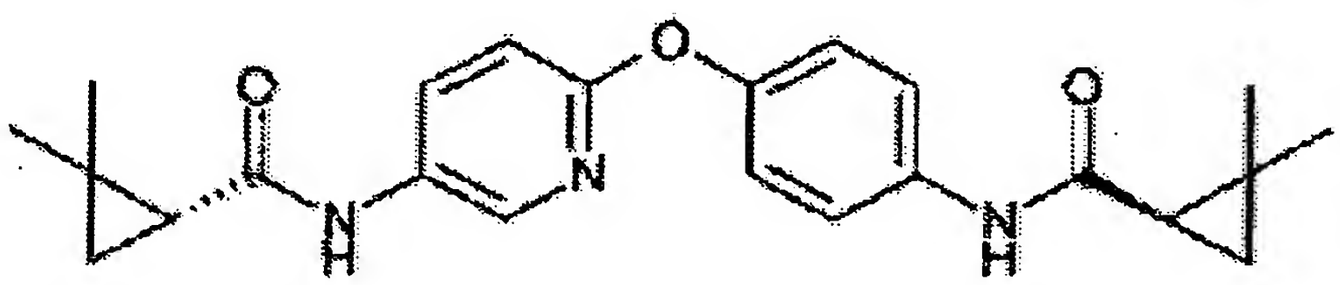
43	
44	
45	
46	

(Example 47)

Evaluation of the NF-kappa B inhibition

Cells used for the tests were those prepared by stably introducing E. coli β-galactosidase (β-gal) genes driven by SV 40 minimum promoter fused with 6 tandems of the NF-KappaB binding motif derived from immunoglobulin kappa light chain enhancer into human normal umbilical cord vein endothelial cells (HUVEC) immortalized with SV 40 large T antigen. The cells were subcultured

in RPMI medium containing 10 % of FBS, and were seeded on a 96-well plate in a concentration of 1 x 10^4/well on a day before the start of the experiments. A compound of the present invention was dissolved in DMSO to obtain a solution of a proper concentration, which was added into the 96-well plate so that the final DMSO concentration would be not higher than 1 %. 30 minutes after the addition of the compound, in order to induce NF-kappa B transcriptional activity, 1 ng/ml of IL-1 β was added to each well so as to obtain the final concentration of 50 ng/ml. β-gal activity was determined 16 hours after with a chemiluminescent substrate (Galacton-Light-Plus: Boehringer Mannheim) according to a protocol attached to the reagent. A Luminescence detector (ATTO) was used for the determination. In this evaluation system, β-gal activity induced by IL-1 β was substantially completely inhibited by glucocorticoid.

In the above evaluation, the compounds of the present invention exhibited the inhibiting effects.

The evaluation results for the compounds of the present invention are shown in Table 1.

Table 1

Test compound	NFkB inhibition activity IC50 (μ g/ml)
Example 1	0．5
Example 2	0．3
Example 3	0．8
Example 4	1
Example 5	0．9
Example 6	0．4
Example 7	1．5
Example 8	1．5
Example 9	0．7
Example 14	0．015
Example 22	0．15
Example 26	0．15

Example 29	1
Example 31	1．5
Example 32	0．1
Example 33	0．2
Example 34	0．3
Example 37	0．09
Example 38	0．05
Example 39	0．035
Example 43	0．25
Example 44	0．1
Example 45	1

(Example 48)

Evaluation of AP-1 inhibition:

Cells used for the tests were those prepared by stably introducing E. coli β-galactosidase (β-gal) genes driven by SV 40 minimum promoter fused with 4 tandems of the AP-1 binding motif derived from human MMP-1 gene enhancer into human normal umbilical cord vein endothelial cells (HUVEC) immortalized with SV 40 large T antigen. The cells were subcultured in RPMI medium containing 10 % of FBS, and were seeded on a 96-well plate in a concentration of 1 x 10^4/well on a day before the start of the experiments. A compound of the present invention was dissolved in DMSO to obtain a solution of a proper concentration, which was added into the 96-well plate so that the final DMSO concentration would be not higher than 1 %. 30 minutes after the addition of the compound, phorbol-12-myristate-13-acetate (PMA) was added to each well so as to obtain the final concentration of 50 ng/ml. β-gal activity was determined 16 hours after with a chemiluminescent substrate (Galacton-Light-Plus: Boehringer Mannheim) according to a protocol attached to the reagent. A Luminescence detector (ATTO) was used for the determination. In this evaluation system, β-gal activity induced by PMA was substantially completely inhibited by glucocorticoid which is a known AP-1 inhibitor.

The compounds of the present invention exhibited the inhibition effect in these tests.

(Example 49)

An antibody titer inhibition test and a delayed-type hyper-sensitivity reaction inhibition test

Rhesus monkeys (female, aged four to six) subjected to the test were sensitized with 6Lf of TTx (Tetanus Toxoid) both in the back skin and in the femur muscle under anesthesia by an intramuscular injection of ketamine. The subject drug at the dose of 50mg/kg had been administered twice daily (7:00am and 7:00pm) for 4 weeks starting at the day of TTx sensitization. The drug was suspended with 0.5% Tween 80 solution and was orally administered using a gastric catheter. The control animals were administered with the vehicle in the same manner as those for the test article. One ml of blood was drawn from femoral vein of each animal twice a week to obtain sera with which the anti-TTx antibody titer was evaluated by the ELISA method. The antibody titer was determined with OD of serially-diluted serum from 1:100 by 2 times and was defined as the degree of dilution reaching to "an average OD of the antibody before immunization +2xSD". One hour after the final administration in the morning on day 28, TTx was challenged once in the thoracic skin (10, 3, 1, 0.3, 0.1, 0.03Lf/ml, 10 μ l/site), and skin reactions at the injection sites were observed 24 and 48 hours after the TTx challenge. The delayed-type hypersensitivity reaction was scored according to the Draize dermal test criteria.

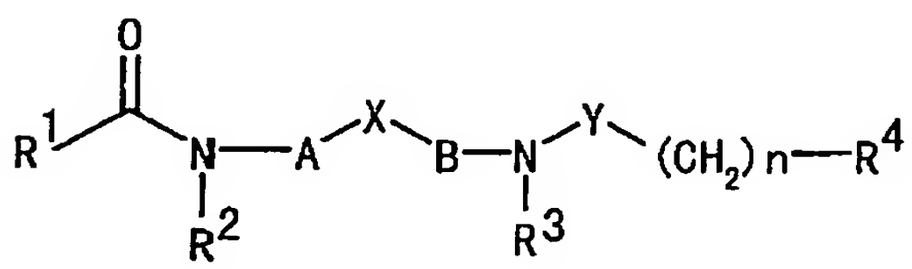
In the above evaluation, the compound of example 43 exhibited its inhibiting effect in both of the antibody titer and the delayed-type hypersensitivity reaction.

As is apparent from the result described above, the compounds of the

activation, and thus are useful in providing the cure against the inflammatory diseases which might be involved in activation of those transcription factors. That is to say, the compounds of the present invention are useful as an anti-inflammatory agent, an anti-rheumatism agent, and immunosuppressive agent, a cancer metastasis inhibitor, and anti-viral agent or a therapeutic agent for arterial sclerosis, which can inhibit a number of gene expression, such as inflammatory cytokines, matrix metalloproteases, inflammatory cell adhesion molecules. Moreover, the compounds of the present invention are advantageously useful because they are free from side effects derived from hormonal action which has been observed in glucocorticoid.

WHAT IS CLAIMED IS:

1. A heterocyclic compound represented by the following general formula (I) and a pharmaceutically acceptable salt thereof:



(I)

wherein R^1 is a cycloalkyl group, a cycloalkyl group having a substituent(s), a cycloalkenyl group or a cycloalkenyl group having a substituent(s); each R^2 and R^3 is a hydrogen atom or an alkyl group; R^4 is an alkyl group, an alkyl group having a substituent(s), an alkenyl group, an alkenyl group having a substituent(s), a cycloalkyl group, a cycloalkyl group having a substituent(s), a cycloalkenyl group, a cycloalkenyl group having a substituent(s), an aryl group, an aryl group having a substituent(s), an aromatic heterocyclic group having at least one hetero-atom within a ring or an aromatic heterocyclic group having a substituent(s) and at least one hetero-atom within a ring; A is a heterocyclic ring or a heterocyclic ring having a substituent(s); B is an aromatic ring, an aromatic ring having a substituent(s), a heterocyclic ring or a heterocyclic ring having a substituent(s); n is an integer selected from 0 to 6; -Y- is an interatomic bond, -CO-, -CO-O-, -CO-NR^5-, -CS-NR^6-, -SO-, -SO_2-, wherein each of R^5 and R^6 respectively is a hydrogen atom or an alkyl group; wherein -X- is an interatomic bond, -O-, -O-CHR^7-, -CHR^8-O-, -O-CO-, -CO-O-, -O-CS-, -CS-O-, -S-, -SO-, -SO_2-, -S-CHR^9-, -CHR^{10}-S-, -S-CO-, -CO-S-, -S-CS-, -CS-S-, -SO_2-NR^{11}-, -NR^{12}-SO_2-, -NR^{13}-, -NR^{14}-CHR^{15}-, -CHR^{16}-NR^{17}-,

-CO-, -C(=NOR^{18})-, -C(=CHR^{19})-,-CO-CHR^{20}-, -CHR^{21}-CO-, -CO-NR^{22}-, -NR^{23}-CO-, -CR^{24}R^{25}-, -CHR^{26}-CHR^{27}-, -CR^{28}=CR^{29}-, -O-CHR^{30}-CHR^{31}-, wherein each of R^{7}, R^{8}, R^{9}, R^{10}, R^{15}, R^{16}, R^{20}, R^{21}, R^{24}, R^{28}, R^{29}, R^{30} and R^{31} respectively is either of a hydrogen atom or an alkyl group; each of R^{11}, R^{12}, R^{13}, R^{14}, R^{17}, R^{18}, R^{19}, R^{22} and R^{23} respectively is either of a hydrogen atom, an alkyl group or an acyl group; each of R^{26} and R^{27} respectively is either of a hydrogen atom, a hydroxy group or an alkyl group; and R^{25} is a hydrogen atom, a hydroxy group, an alkyl group, an alkyl group having a substituent(s), a mercapto group, an alkoxy group, an alkylthio group, an acyloxy group, an amino group, an alkylamino group, an amino group substituted with an amino protective group, a carboxyl group, an alkoxycarbonyl group, an aminocarbonyl group, or a cyano group.

2. The heterocyclic compound and pharmaceutically acceptable salt thereof according to claim 1, wherein R^{1} in the general formula (I) is a cycloalkyl group having a substituent(s).

3. The heterocyclic compound and pharmaceutically acceptable salt thereof according to claim 1, wherein R^{1} of the general formula (I) is a cyclopropyl group having a substituent(s).

4. The heterocyclic compound and pharmaceutically acceptable salt thereof according to claim 1, wherein R^{1} of the general formula (I) is either of a 2,2-dimethylcyclopropyl group, a 2,2-dichlorocyclopropyl group, a 2,2-difluorocyclopropyl group or a 2,2-dibromocyclopropyl group.

5. The heterocyclic compound and pharmaceutically acceptable salt thereof according to claim 4, wherein, in the general formula (I), A is either of an aromatic heterocyclic ring or an aromatic heterocyclic ring having a substituent(s), and B is either of an aromatic ring, an aromatic ring having a substituent(s), an aromatic heterocyclic ring or an aromatic heterocyclic ring having a substituent(s).

6. The heterocyclic compound and pharmaceutically acceptable salt thereof

according to claim 5, wherein –Y- of the general formula (I) is an interatomic bond, –CO-, -CONR^5-, CSNR^6- or –SO_2-, wherein each of R^5 and R^6 respectively is a hydrogen atom or an alkyl group.

7. The heterocyclic compound and pharmaceutically acceptable salt thereof according to claim 1, wherein, in the general formula (I), –X- is an interatomic bond, –O-, -O-CHR^7-, -CHR^8-O-, -S-, -NR^{13}-, -CR^{24}R^{25}- or –O-CHR^{30}-CHR^{31}-, wherein each of R^7, R^8, R^{24}, R^{30} and R^{31} respectively is a hydrogen atom or an alkyl group; R^{13} is either of a hydrogen atom, an alkyl group or an acyl group; and R^{25} is a hydrogen atom, a hydroxy group, an alkyl group, an alkyl group having a substituent(s), a mercapto group, an alkoxy group, an alkylthio group, an acyloxy group, an amino group, an alkylamino group, an amino group substituted with an amino protective group, a carboxyl group, an alkoxycarbonyl group, an aminocarbonyl group, or a cyano group.

8. The heterocyclic compound and pharmaceutically acceptable salt thereof according to claim 7, wherein, in the general formula (I), A is either of a pyridine, a pyridazine, a pyrimidine, a pyridine having a substituent(s), a pyridazine having a substituent(s) or a pyrimidine having a substituent(s); and B is a benzene ring or a benzene ring having a substituent(s).

9. The heterocyclic compound and pharmaceutically acceptable salt thereof according to claim 8, wherein R^1 and R^4 of the general formula (I) may be the same or different from each other and each may be either of a 2,2-dimethylcyclopropyl group, a 2,2-dichlorocyclopropyl group, a 2,2-difluorocyclopropyl group or a 2,2-diburomocyclopropyl group; –Y- is –CO-; and n is 0.

10. The heterocyclic compound and pharmaceutically acceptable salt thereof according to claim 8, wherein R^1 of the general formula (I) is either of a 2,2-dimethylcyclopropyl group, a 2,2-dichlorocyclopropyl group, a 2,2-difluorocyclopropyl group or a 2,2-dibromocyclopropyl group; R^4 is an aryl group or

an aryl group having a substituent(s); –Y- is –CO-; and n is an integer selected from 1 to 3.

11. The heterocyclic compound and pharmaceutically acceptable salt thereof according to claim 8, wherein R^1 of the general formula (I) is either of a 2,2-dimethylcyclopropyl group, a 2,2-dichlorocyclopropyl group, a 2,2-difluorocyclopropyl group or a 2,2-dibromocyclopropyl group; R^4 is an aryl group or an aryl group having a substituent(s); -Y- is an interatomic bond; and n is an integer selected from 2 to 4.

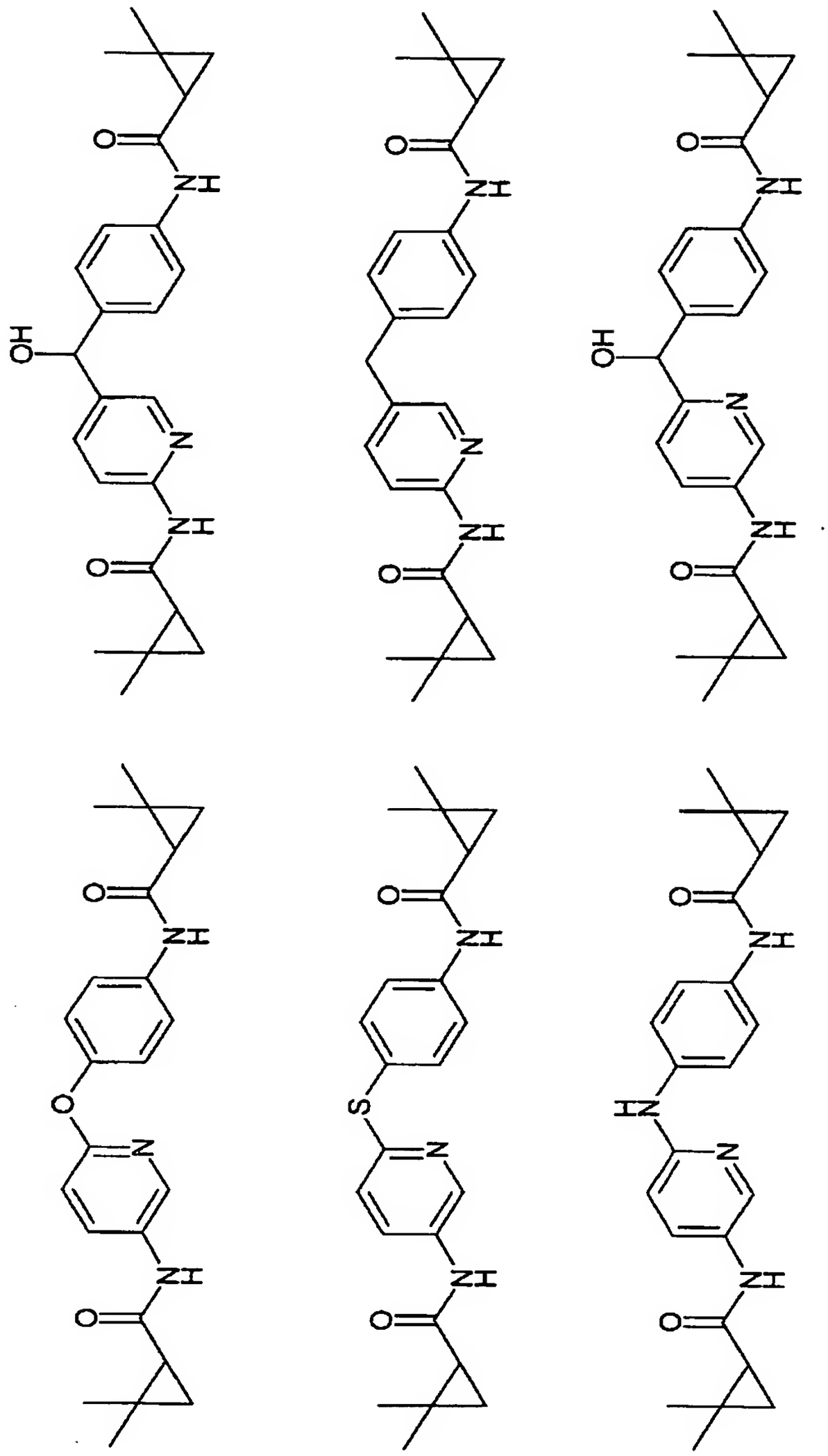
12. The heterocyclic compound and pharmaceutically acceptable salt thereof according to any one of claims 3 to 11, wherein when R^1 of the general formula (I) is a cyclopropyl group having a substituent(s), an absolute configuration of the carbon atom on the cyclopropyl group adjacent to the carbonyl group is S.

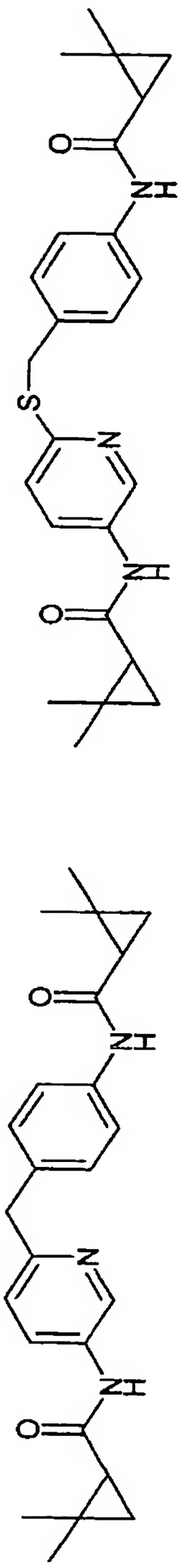
13. The heterocyclic compound and pharmaceutically acceptable salt thereof according to any one of claims 3 to 11, wherein when R^1 of the general formula (I) is a cyclopropyl group having a substituent(s), an absolute configuration of the carbon atom on the cyclopropyl group adjacent to the carbonyl group is R.

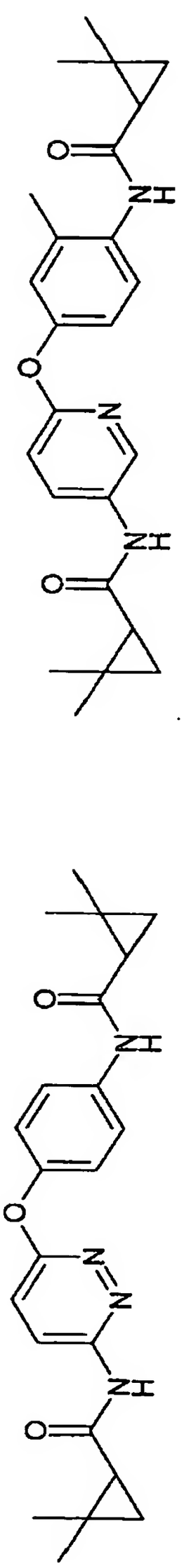
14. The heterocyclic compound and pharmaceutically acceptable salt thereof according to claim 9, wherein when each of R^1 and R^4 of the general formula (I) is a cyclopropyl group having a substituent(s), an absolute configuration of the carbon atom on the cyclopropyl group adjacent to the carbonyl group is S.

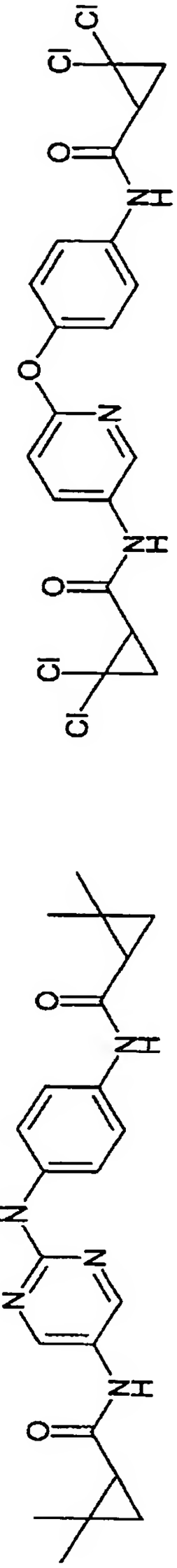
15. The heterocyclic compound and pharmaceutically acceptable salt thereof according to claim 9, wherein when each of R^1 and R^4 of the general formula (I) is a cyclopropyl group having a substituent(s), an absolute configuration of the carbon atom on the cyclopropyl group adjacent to the carbonyl group is R.

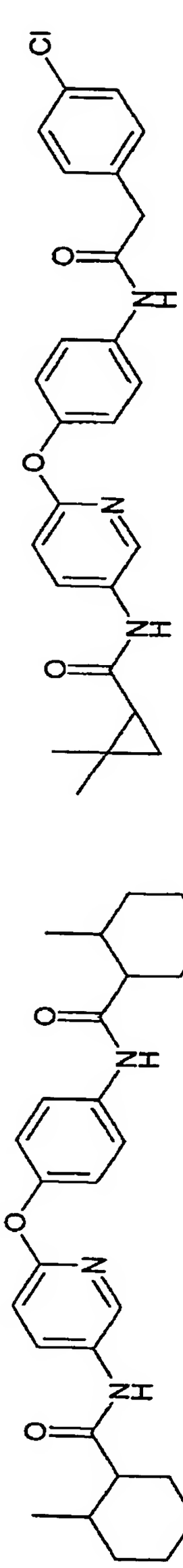
16. A heterocyclic compound and a pharmaceutically acceptable salt thereof represented by the following formulas:

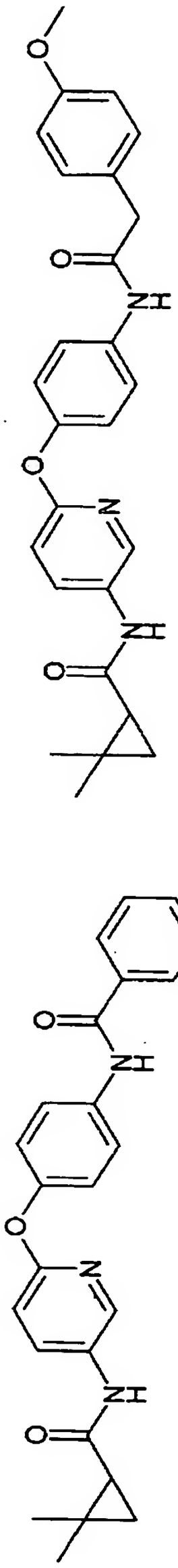


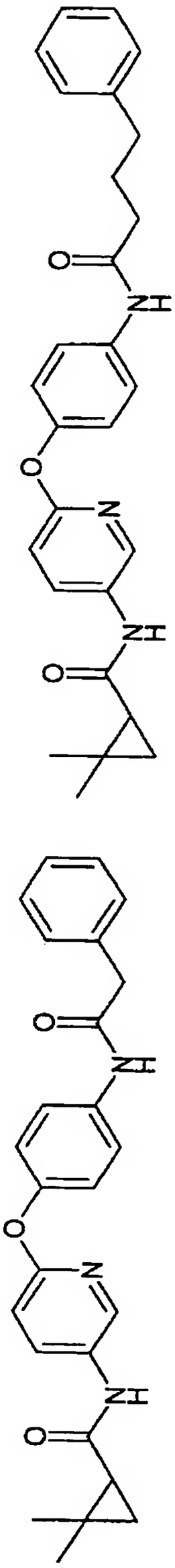


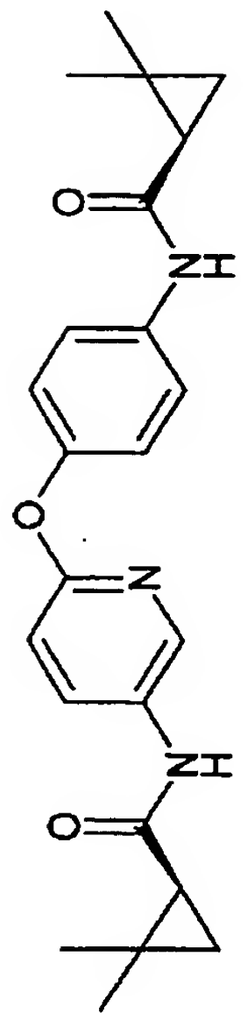
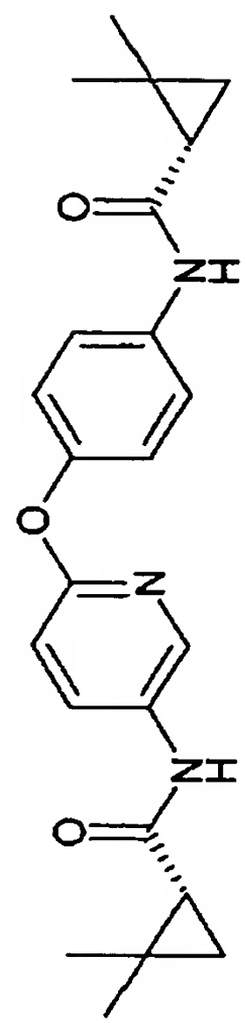
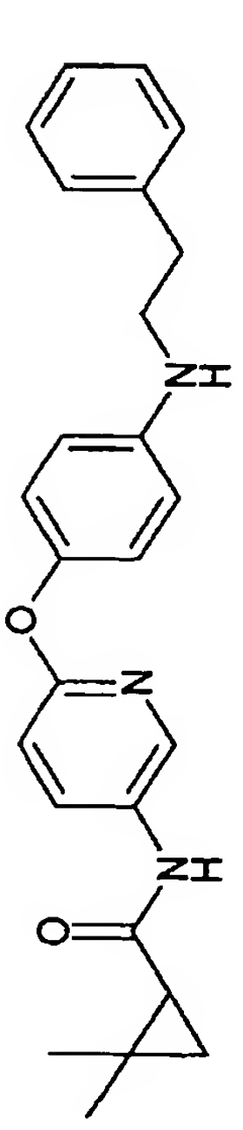
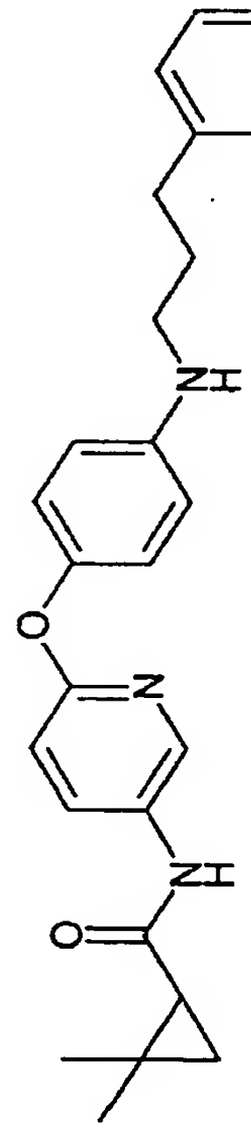
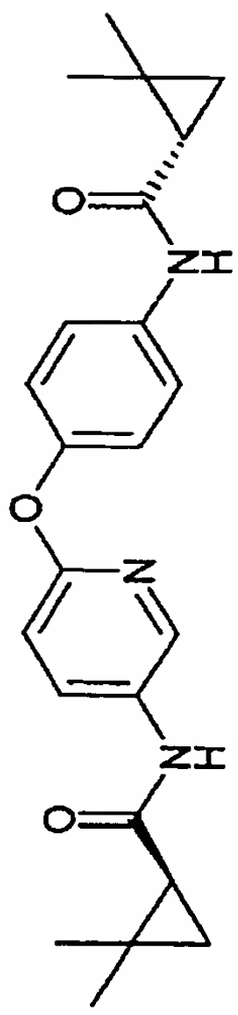










17. The heterocyclic compound and pharmaceutically acceptable salt thereof according to claim 1, wherein B is a phenylene group; R^1 is a cycloalkyl group

having a substituent(s) or a cycloalkenyl group having a substituent(s); R^2 is a hydrogen atom or an alkyl group; R^3 is a hydrogen atom or an alkyl group; R^4 is an alkyl group which may be substituted, a cycloalkyl group which may be substituted, a cycloalkenyl group which may be substituted, an aryl group which may be substituted or an aromatic heterocyclic ring group which may be substituted and also has one or more hetero atoms; -X- is –O-, -O-CHR^7-, -CHR^8-O-, -O-CO-, -CO-O-, -O-CS-, -CS-O-, -S-, -SO-, -SO_2-, -S-CHR^9-, -CHR^{10}-S-, -S-CO-, -CO-S-, -S-CS-, -CS-S-, -SO_2-NR^{11}-, -NR^{12}-SO_2-, -NR^{13}-, -NR^{14}-CHR^{15}-, -CHR^{16}-NR^{17}-, -CO-, -C(=NOR^{18})-, -C(=CHR^{19})-, -CO-CHR^{20}-, -CHR^{21}-CO-, -CO-NR^{22}-, -NR^{23}-CO-, -$CR^{24}R^{25}$-, -CHR^{26}-CHR^{27}- or -CR^{28}=CR^{29}, wherein each of R^7, R^8, R^9, R^{10}, R^{20}, R^{21}, R^{24}, R^{28} and R^{29} is either of a hydrogen atom or an alkyl group; each of R^{11}, R^{12}, R^{13}, R^{14}, R^{17}, R^{18}, R^{19}, R^{22} and R^{23} is either of a hydrogen atom, an alkyl group or an acyl group; each of R^{15} and R^{16} is a hydrogen atom or an alkyl group; each of R^{26} and R^{27} is either of a hydrogen atom, a hydroxy group or an alkyl group; and R^{25} is a hydrogen atom, a hydroxy group, an alkyl group which may be substituted, a mercapto group, an alkoxy group, an alkylthio group, an acyloxy group, an amino group which may be substituted with an alkyl group or an amino protective group, a carboxyl group, an alkoxycarbonyl group, an aminocarbonyl group, or a cyano group; wherein n is an integer selected from 0 to 6; Y is –C(O)-; and A is the aromatic heterocyclic ring including at least one or more nitrogen atom.

18. A pharmaceutical composition comprising as an active ingredient a heterocyclic compound or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 17.

19. An AP-1 activation inhibitor or a NF-kappaB activation inhibitor comprising as an active ingredient a heterocyclic compound or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 17.

20. An inflammatory cytokine production inhibitor, a production inhibitor

for matrix metalloprotease or an inflammatory cell adhesion factor expression inhibitor comprising as an active ingredient a heterocyclic compound or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 17.

ABSTRACT

The present invention provides an AP-1 activation inhibitor, a NF-kappaB activation inhibitor, an inflammatory cytokine production inhibitor, a production inhibitor for matrix metalloprotease or an inflammatory cell adhesion factor expression inhibitor, which contains a heterocyclic compound or a pharmaceutically acceptable salt thereof as an active ingredient.